«Оңтүстік Қазақстан медицина академиясы» акционерлік қоғамы

ӘӨЖ 616.74-007.23-002 Қолжазба құқығында

АУАНАСОВА АКЕРКЕ ТУРЕБЕКОВНА

«Қазіргі кезеңдегі жүйелі васкулиттер: клиникалық-зертханалық сипаттама және науқастарды жүргізу стратегиясын оңтайландыру»

8D10141 «Медицина»

Философия докторы (PhD)
дәрежесін алуға арналған диссертация

Отандық ғылыми кеңесшісі:
медицина ғылымдарының кандидаты,
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Қазақстан Республикасы,
Шымкент 2024 жыл

Мазмұны

Clinical Rheumatology (2023) 42:2761–2775
https://doi.org/10.1007/s10067-023-06694-6

REVIEW ARTICLE

New-onset systemic vasculitis following SARS-CoV-2 infection and vaccination: the trigger, phenotype, and outcome

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Received: 19 May 2023 / Revised: 13 June 2023 / Accepted: 2 July 2023 / Published online: 8 July 2023

Abstract

The global health crisis caused by the COVID-19 pandemic overwhelmed the capacity of healthcare systems to cope with the rapidly spreading infection and its associated complications. Among these complications, autoimmune phenomena such as systemic vasculitis emerged as a significant challenge. Both the SARS-CoV-2 virus and the vaccines developed to combat it appeared to induce clinical manifestations resembling various types of systemic vasculitis, affecting large, medium, and small vessels. These virus- or vaccine-induced vasculitides exhibited a distinct natural history and course from de novo vasculitis, as they were more responsive to steroid therapy and some mild cases even resolved spontaneously. Notably, there have been no confirmed cases of SARS-CoV-2 infection or vaccination triggering variable vessel vasculitis like Behcet's disease or Kawasaki disease. IgA vasculitis, which is predominantly a pediatric condition, was more prevalent in adults after COVID-19 infection and they had a favorable outcome with glucocorticoid treatment. The impact of immunosuppression, especially B-cell-depleting agents, on the immunogenicity of the vaccine was evident, but there was no significant increase in the incidence of SARS-CoV-2 infection in these patients compared to the general population. Considering their relatively benign course, these post-COVID or post-vaccine vasculitides seem to be amenable to 0.8 to 1 mg/kg prednisolone or equivalent, which could be gradually tapered. The need for immunosuppression and the duration of steroid therapy should be determined on an individual basis. While the world still reels from the perils of a deadly pandemic, the aftermath continues to haunt. Our narrative review aims to explore the effects of COVID and the vaccine on systemic vasculitis, as well as the effect of disease and immunosuppression on the immunogenicity of the COVID vaccine.

Keywords COVID-19 · Rheumatic disease · Secondary vasculitis · Vaccination · Vasculitis

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected nearly 700 million people across the world and crippled healthcare and economies alike [1]. The ripples of the coronavirus disease (COVID-19) pandemic are still affecting populations worldwide. Though mortality has come down after the advent of vaccinations, there are still emerging mutations and strains. These have a continued effect on healthcare systems and are possibly associated with the emergence of autoimmune diseases [2].

Considering the higher incidence of thrombosis in COVID-19 patients and the reported mortality benefit with heparin [3], the disease was presumed to create a pro-thrombotic milieu, which may be explained in terms of dysregulation of Virchow's triad (stasis, vascular damage, and hypercoagulation) [4, 5]. The normal healthy vascular endothelium maintains laminar blood flow through the vessels, which prevents microvascular damage. However, when the homeostatic laminar blood flow turns turbulent, there are micro damages to the endothelium, which exposes the subendothelial collagen and von-Willebrand factor (vWF) and favors the formation of a platelet–fibrin thrombus, which may progress to vascular obstruction. Also, there are hints of involvement of the bradykinin system and the renin-angiotensinogen-aldosterone axis which all induce pro-inflammatory changes in the vascular endothelium [6]. The hyper-inflammatory state itself in acute SARS-CoV-2 infection contributes to thrombosis and hypercoagulability by increased expression of platelet-derived growth factor (PDGF), vWF, and platelet-activating factor (PAF) [5], which may result in vasculopathy and possibly vasculitis. The other explanation for the pathogenesis of vasculitis and thrombosis, particularly of antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) post-COVID-19, could be over-activation of neutrophils, with the resultant formation of neutrophil extracellular traps (NETs), which can eventually lead to thrombosis; and if this is combined with co-existent anti-phospholipid antibodies, the thrombotic risk only rises [7].

Infection, as a putative trigger for vasculitis, is not a new concept. Some of the infections known to be associated with vasculitis include common viruses like hepatitis B, hepatitis C, human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), herpesviruses, and dengue virus and bacteria like *Streptococci*, *Staphylococci*, *Mycobacterium*, *Brucella*, and *Borrelia* [8–10]. IgA vasculitis usually has a history of a preceding upper respiratory infection in nearly 35–60% of the cases [11]. Recently added to the list is the SARS-CoV-2 infection which was reported to trigger almost every phenotype of vasculitis, including large-, medium-, and small-vessel disease [12]. Among the many theories proposed for the causation of vasculitis by SARS-CoV-2, the theory of virus-triggered autoimmunity causing thrombosis and vasculopathy is the most accepted and well-described.

A possible hypothesis for vasculitis or autoimmune phenomenon triggered by vaccine could be autoimmune/inflammatory syndrome induced by adjuvant (ASIA); however, the latent period from the administration of vaccine to the development of symptoms tends to be longer for systemic vasculitis occurring post-COVID vaccine, as opposed to the hyperacute onset of symptoms with ASIA [13].

We had previously explored the relationship between COVID-19, thrombosis, and vasculopathy [4] and had also hypothesized how COVID-19 may precipitate autoimmune rheumatic diseases [14]. Based on this preliminary work, we also investigated post-COVID-19 reactive arthritis [15]. Taking this forward, here we have attempted to review the link between COVID-19 and various vasculitides. The complications of COVID are manifold and we are only touching the tip of the iceberg in exploring and understanding the havoc it wrecks on the immune system. With this narrative review, we aim to add value to the existing concept of SARS-CoV-2 or its vaccine as a possible putative trigger for autoimmunity, systemic vasculitis in particular, and explore the pleiotropism of its phenotypes.

Search strategy

A thorough search of PubMed/MEDLINE, LitCovid, and Scopus databases was employed with keywords including "COVID-19," "vaccine," "vasculitis," "large vessel vasculitis," "giant cell arteritis," "Takayasu arteritis," "medium vessel vasculitis," "Kawasaki disease," "IgA vasculitis," "ANCA vasculitis," "small vessel vasculitis," "Behcet's disease/syndrome," and "infection" in various combinations. Only articles available in English were collated for the review and authors selected the case reports and case-based reviews that were comprehensively written with adequate information and description of the case, and came under the purview of our review based on their experience, as is recommended by the standard recommendations for writing a narrative biomedical review [16].

Large-vessel vasculitis

Large-vessel vasculitides (LVV) (giant cell arteritis — GCA and Takayasu arteritis — TAK) are some of the more common forms of systemic vasculitis, with TAK being particularly common in India and other Southeast Asian countries. While TAK predominates in young females, GCA is classically described as a disease of the elderly (> 50 years). As

GCA and SARS-CoV-2 infection may have some overlapping clinical features like fever, headache, fatigue, and malaise, it is vital to promptly differentiate the two as GCA with the threat of imminent visual loss demands immediate intervention with high-dose steroids. With COVID-19, the incidence of vasculitis increased, with many cases of LVV being reported following the infection or vaccination (Table 1).

A recent systematic review addressing this clinical overlap between GCA and COVID-19 described that though constitutional symptoms like headache, fever, and malaise were common to both, the classical features of GCA like jaw claudication, trismus, visual loss, scalp tenderness, or weight loss were not reported in COVID-19 [26]. Fever was also more common in COVID-19 (83% of the patients), as opposed to GCA (27%) [26].

Patients of previously diagnosed de novo GCA were observed to have a worse clinical outcome of COVID-19. A large multicenter French cohort observing the severity, outcome, and mortality of GCA patients who developed a SARS-CoV-2 infection noted that these patients had a higher odds ratio to develop severe COVID-19 in comparison with RA, and the mortality was at 17.8% [27]. In this cohort, patients who were on rituximab-based therapy were excluded. One possible explanation for the worse outcomes in GCA could be the older age of these patients and the associated comorbidities like diabetes mellitus, hypertension, and coronary heart disease, which may act as additional risk factors for a worse COVID-19 outcome.

Not only the infection but also the COVID-19 vaccine has been implicated in the causation of LVV, like GCA. The GCA that occurs post-vaccine had a shorter latent period of 1–5 days, as opposed to post-SARS-CoV-2 infection, which usually occurred with a longer latency of around 2–4 weeks (Table 1). Post-vaccine GCA was more commonly reported with BNT162b2—Pfizer-BioNTech mRNA vaccine and mostly had a good prognosis with complete resolution of symptoms with early optimal treatment with high dose systemic glucocorticoids [17, 20–23, 25].

While the most common LVV with COVID-19 was GCA, Takayasu arteritis (TAK) has also been reported [19]. A keen eye is needed to distinguish the symptoms of GCA from COVID-19. Usually immediate intervention has a good prognosis with a near-complete resolution of symptoms in most. As opposed to de novo LVV, those occurring post-COVID-19 or vaccine had a good response to glucocorticoids and a better prognosis overall (Table 1).

Medium-vessel vasculitis

Kawasaki disease (KD) was the most frequently reported and described medium-vessel vasculitis (MVV) in the context of COVID-19. KD is one of the most common childhood vasculitides, more prevalent in Asian countries, mainly Japan and Korea. Children are mostly affected, from infancy to adolescence, and it can progress to deadly coronary aneurysms if left untreated. Table 2 summarizes the isolated case reports of KD that were triggered by an antecedent SARS-CoV-2 infection.

The issue with diagnosing KD after COVID-19 in children is the hyper-inflammatory syndrome that is similar to atypical KD, termed multisystem inflammatory syndrome in children (MIS-C) [34]. Most of these cases had been described as an incomplete KD occurring in children with severe COVID-19. However, there are a few fundamental differentiating features: KD mostly affects children under the age of 5 years, while COVID-MIS-C was observed to be more frequent in school-going children [35]. Additionally, myocardial involvement was more frequent in patients with MIS-C, as opposed to KD, where there are coronary aneurysms in severe untreated disease, which can cause secondary myocardial involvement. Clinical features of importance that overlapped with KD and MIS-C included fever (100%), gastrointestinal symptoms (77%), conjunctival injection (49.7%), rash (54%, mostly maculopapular), mucous membrane changes (43%), and peripheral skin changes (18.9%), while a small portion of them had also developed shock (12.1%) (30). However, features like lymphadenopathy and desquamation that are seen frequently in KD were rare in MIS-C (8% and 5.5% respectively) [36]. Also, children with MIS-C do not appear to have any long-term sequelae on follow-up and may have complete resolution even of their myocardial abnormalities [37].

However, cases of classic KD have also increased during the pandemic. Infectious triggers have been long postulated in the pathogenesis of KD. Along these lines, SARS-CoV-2 acting as a putative trigger for KD-like disease is also hypothesized. A French cohort of 230 KD patients described a rate of hospitalization of 1.2 cases per month in the pre-pandemic era; however, with the onset of the COVID-19, there was a sharp rise in the number of hospitalizations for KD to 6 cases per month, which was a substantial 497% increase [95% CI 72–1082]. The facts that SARS-CoV-2 was the virus responsible for most infections during that period, and 80% of these KD patients had COVID-19 with a positive RT-PCR, strongly pointed towards SARS-CoV-2 being the trigger for KD [38]. However, two other cohorts from China and Japan showed contradicting results with no clear increase in cases of KD during the pandemic; in contrast, the Japanese cohort reported a decrease in the number of reported KD cases during the course of the pandemic, which they attributed to a lesser incidence of other viral infections which were a possible trigger, owing to the social distancing and masking mandates [39, 40].

Individual case reports of KD occurring following a SARS-CoV2-2 trigger are summarized in Table 2. As opposed to LVV post-COVID that had a latent period after

Table 1 Large-vessel vasculitis following SARS-CoV2 infection and/or COVID-19 vaccine (isolated case reports are summarized in the table, while case series and cross-sectional studies are described in the text)

Author	Age/sex	Type of LVV	Clinical features	SARS-CoV-2 infection/vaccination	Latent period	Biopsy	Imaging of vessels	Treatment	Outcome
Mejren et al. [17]	62Y/F	GCA	Fatigue, night sweats, loss of appetite, weight loss ~ 4 kg	Pfizer-BioNTech COVID-19 vaccine (2 doses, 3 weeks apart)	1–2 days	NA	CT: diffuse wall thickening of the aorta, bilateral CIA, left SCA, proximal BCA Vascular USG: segmental hypoechoic wall thickening of bilateral AA	40 mg PDN	Improvement at 2 weeks
Szydełko-Paśko et al. [18]	69Y/F	GCA	Fever, fatigue, cough, complete visual loss in the left eye, severe headache — retro-orbital, occipital, scalp tenderness	SARS-CoV-2 infection (RT-PCR)	2.5 weeks	NA	Vascular USG of temporal artery: wall thickening, "halo" sign, thrombosis of ciliary arteries	LMWH for 10 days, PDN 80 mg/day for 3 days, tapered to 60 mg/day	No improvement in the left eye vision
Mendes et al. [19]	19/F	TAK	Fatigue, malaise, chest and low back pain	SARS-CoV-2 infection	1 month	NA	Concentric and diffuse thickening of the descending thoracic and AA with progression along the proximal half of both CIA and renal arteries	60 mg PDN tapered by 5 mg every 2 weeks	Complete resolution of symptoms and acute phase response
DK Ishizuka et al. [20]	74/M	GCA	Temporal headache, cough	BNT162b2 mRNA COVID-19 vaccine (3rd dose)	1 month	NA	PET/CT showed hyperaccumulation in the thoracic aorta, SCA, axillary, brachial, and temporal arteries	30 mg prednisolone	Improvement
M Gilio et al. [21]	63/F	GCA	Fatigue, malaise, low-grade fever, arthralgia, headache, stiffness at shoulders and neck	mRNA COVID-19 vaccine (BNT162b2—Pfizer-BioNTech) — 1st dose	1 day	NA	FDG/PET: vasculitis with large artery involvement of carotid, SCA	50 mg PDN, tapered	Symptoms resolved; acute phase response subsided

Table 1 (continued)

Author	Age/sex	Type of LVV	Clinical features	SARS-CoV-2 infection/vaccination	Latent period	Biopsy	Imaging of vessels	Treatment	Outcome
Anzola et al. [22]	83/F	GCA	Cervical pain, headache, scalp tenderness	COVID-19 mRNA (BioNTech/Pfizer) vaccine — 1st dose	1 day	NA	Vascular USG showed a non-compressible halo sign in the parietal branch of the right temporal artery. FDG-PET/CT: bilateral vertebral vasculitis	High-dose steroids	Clinical improvement and remission with weekly methotrexate and low-dose steroid
T. Gambichler et al. [23]	82/M	GCA with skin necrosis	Headache, jaw claudication, weight loss, bilateral temporoparietal skin necrosis, and near-total visual loss	SARS-CoV-2 vaccination (BTN162b2) — 2nd dose	10 days	Findings coexistent with GCA	Vascular USG showed halo sign, non-compressible in bilateral temporal arteries	NA	NA
Sauret et al. [24]	70/M	GCA	Headache, scalp tenderness	ChAdOx1 nCoV-19 SARS-CoV-2 vaccine (AZD1222) — 1st dose	Few days	Temporal artery: intima thickening, fragmentation of internal elastic lamina, and moderate infiltration of the media with giant cells	CECT, FDG-PET normal	0.5 mg/kg/day prednisolone	Near-complete improvement in symptoms in 2 days
Aoki et al. [25]	81/M	GCA	Fever, headache	BNT162b2 mRNA vaccine — 2nd dose	30 days	NA	FDG-PET showed an increased uptake by the large vessels, especially the bilateral brachial, SCA, and carotid arteries	Naproxen for 2 weeks, antipyretic	Resolved in 2 weeks

AA, abdominal aorta; *BCA*, brachiocephalic artery; *CIA*, common iliac artery; *CECT*, contrast-enhanced computed tomography; *FDG-PET*, fluorodeoxyglucose positron emission tomography; *GCA*, giant cell arteritis; *LMWH*, low molecular weight heparin; *LVV*, large-vessel vasculitis; *PDN*, prednisolone; *RT-PCR*, real-time polymerase chain reaction; *SCA*, subclavian artery; *USG*, ultrasonography; *NA*, not available

Table 2 Summary of cases of KD reported in association with SARS-CoV-2 infection

Authors	Age/sex	SARS-CoV-2 diagnosis	Criteria clinical features	Imaging	Treatment	Outcome
Shala et al. [28]	14/M	Elevated IgG levels	Generalized rash, bilateral nonexudative conjunctivitis, peripheral extremity swelling, cervical lymphadenopathy Also had right hemiparesis	MRI brain — acute infarct in the left MCA territory. Transcranial duplex ultrasound — suggesting distal resistance (resulting from the occluded terminal branches of left MCA)	IVIG (2 g/kg), low-dose aspirin, 40 mg methylprednisolone twice daily	Near complete resolution of neurological symptoms within 48 hours
Khan et al. [29]	8/M	High IgG titers	Fever, bilateral non-purulent conjunctivitis, generalized maculopapular eruptions, pedal edema Also, had tachypnea, desaturation	Chest X-ray — non-homogenous opacities in the left lower zone	Antibiotics, IVIG (2 g/kg), high-dose aspirin	Resolution of respiratory distress, fever by 24 hours of IVIG
Labe et al. [30]	6/M	RT-PCR positive	Fever, cheilitis, extremity rash, non-purulent bilateral conjunctivitis	NA	NA	Complete clinical improvement at 2 weeks
Labe et al. [31]	3/M	Close contact with COVID-19 patient	Fever, generalized exanthem, bilateral nonexudative conjunctivitis, cheilitis, stomatitis	CT chest — ground glass opacities and right posterobasal consolidation	IVIG (2 g/kg)	Complete resolution in 1 week
Manion et al. [32]	30-month-old/F	RT-PCR positive	Fever, diffuse macular rash, cheilitis, edema of hands — 1st episode 2nd episode — after 3 days post-discharge with fever, flushed cheeks New anemia, thrombocytopenia	Echo normal at presentation Repeat echo at 2nd hospitalization — mildly dilated left anterior descending artery. LAD *z*-score 3	IVIG, low-dose aspirin at 1st hospitalization IVIG repeated in 1 week at 2nd hospitalization	Clinical improvement at 2 days after 2nd dose of IVIG
Tahir et al. [33]	7 months/M	IgM positive	Fever, non-pruritis maculopapular rash, non-exudative conjunctivitis, strawberry tongue, swelling of lips, tonsillar enlargement	Echo — dilated left and right coronary arteries	IVIG (2 g/kg), high-dose aspirin, IV methylprednisolone for 3 days	Marked improvement after 1 week, echo normal at 6 weeks

IVIG, intravenous immunoglobulin G; *LAD*, left anterior descending; *MCA*, middle cerebral artery

the SARS-CoV2 infection, KD began with the viral infection. COVID vaccination, however, has not been reported or linked to the development of KD.

ANCA-associated vasculitis

ANCA-associated vasculitis (AAV) is one of the more rapidly progressive types of systemic vasculitis and has a poorer prognosis unless intervention with adequate aggressive immunosuppression is instituted early-on. Based on organ involvement, pathological features, and the antibody association, they can be classified into granulomatosis with polyangiitis (GPA) associated mostly with anti-proteinase-3 (anti-PR3) antibodies, or eosinophilic granulomatosis with polyangiitis (EGPA) or microscopic polyangiitis (MPA) associated mostly with anti-myeloperoxidase (anti-MPO) antibodies. The onset of AAV can be concomitant with a severe SARS-CoV-2 infection or following the infection, though most of the cases described had their onset with the infection (summarized in Table 3). The incidence of AAV was overall increased during the pandemic; however, there were many factors that affected this. During the pandemic, most of these patients went to general practitioners and physicians; but, the awareness among physicians about recognizing the smaller signs of disease or flare was not robust.

The phenotype of the cases of AAV post-COVID or post-vaccine varied, and it was more severe than the other types of vasculitis described earlier. It ranged from mild organ-limited vasculitis to the severe life-threatening complications of diffuse alveolar hemorrhage which needed aggressive management with plasma exchange and rituximab [42, 45, 52, 53]. However, severe lung involvement was not associated with vaccination. The Pfizer-BioNTech mRNA vaccine was most commonly implicated in the causation of AAV, though there were also isolated reports of the Oxford AstraZeneca and Johnson & Johnson vaccines resulting in AAV [50, 54, 55] — but this has to be viewed in the light of the relative use of each of these vaccines. Indeed, these were milder forms of disease, but one patient reported rhabdomyolysis with glomerulonephritis and severe acute tubular necrosis following the Pfizer vaccine [56]. AAV following COVID was uncommon in childhood, with scarce literature and overall children and adolescents had a milder disease with good response to immunosuppression [52, 56, 57].

The other aspect during AAV in the setting of COVID-19 is the effect of immunosuppression, especially the B-cell-depleting therapies like rituximab on vaccine efficacy. During the pandemic, some clinicians across the USA and Europe (Johns Hopkins, Preston) decided to defer the dose of rituximab and postponed the maintenance doses to prevent the risk of severe COVID [58]. Out of the 206 patients of AAV who were on rituximab or cyclophosphamide, rituximab was postponed in 21 patients and 12 of them had a disease relapse. Despite all patients following strict personal protective measures and quarantining, they observed that the incidence of COVID-19 in them did not differ from the general population; however, delaying the immunosuppression resulted in a flare in more than 50% of the patients and hence the group opined that immunosuppression was to be continued during the pandemic and deferring the dosing was counterproductive [58]. Added to this was the issue of low immunogenicity of the SARS-CoV-2 vaccine in patients with AAV on rituximab. The timing of the vaccine to obtain the optimal antibody response was uncertain. Evidence from rheumatoid arthritis (RA) patients on rituximab who received an influenza vaccine showed a lack of adequate antibody response even after 2 months of rituximab; however, the group of patients who received the vaccine 6–10 months after the last dose of rituximab exhibited a robust antibody response [59]. AAV patients on rituximab take a considerably longer time for B-cell repopulation; hence, it is prudent to allow at least 6 months between the SARS-CoV-2 vaccine and the next rituximab dose [60].

Another pressing issue that was recognized by us via an online survey was that physicians were not fully competent in recognizing all the signs and symptoms of AAV and < 50% of the surveyed practitioners were confident of identifying all the organ manifestations, which may contribute to some cases of organ-limited AAV being missed [12].

Some of the distinct case reports of AAV following infection or vaccination have been summarized in Table 3.

IgA vasculitis

IgA vasculitis (IgAV) is the most common childhood vasculitis, though it can occur in adulthood. IgAV is mostly known to be associated with an antecedent infection or some environmental trigger. This is one of the most reported cases of systemic vasculitis triggered by SARS-CoV-2 infection and vaccination alike. IgAV following COVID-19 is different from de novo IgAV in the sense that it mostly involves adults, with a median age of 23 years; major organ involvement is limited and there is a good response to glucocorticoids [61]. The presenting features, including atypical features, and the outcome of IgAV post-COVID infection or vaccination are summarized in Table 4.

Variable vessel vasculitis — focus on Behcet's disease

Behcet's disease (BD) is the prototype variable vessel vasculitis (VVV). Interestingly, as opposed to the other types of vasculitides, there is no report of BD occurring

Table 3 Summary of case reports of AAV following SARS-CoV-2 infection or vaccination

Author	Age/sex	SARS-C0V-2 infection/vaccine	Clinical features	Anti-MPO/anti-PR3	Renal involvement	Biopsy	Treatment	Outcome
Uppal et al. [41]	64/M	RT-PCR positive	Progressive dyspnea and cough for 2 weeks	Anti-MPO	S.Cr 7.87 mg/dl	Kidney — pauci-immune glomerulonephritis; IF: non-specific	Pulse methylprednisolone 500 mg for 3 days, 1 g rituximab after a negative RT-PCR for SARS-CoV-2	Clinical improvement, reduction in S.Cr to 2.4 mg/dl
Uppal et al. [41]	46/M	RT-PCR positive	Fever, cough, diffuse purpuric rash	Anti-PR3	SCr 4 mg/dl, 100 mg/dl protein, moderate RBCs	Kidney — focal necrotizing glomerulonephritis. IF: trace mesangial staining for IgA, IgM, C3	Pulse methylprednisolone 1 g for 3 days, rituximab 375 mg/m^2	Decreased SCr to 1.2 mg/dl, at 12 weeks follow-up
Moeinzadeh et al. [42]	25/M	RT-PCR positive	Fatigue, arthralgia, rhinorrhea, progressive dyspnea (DAH)	Anti-PR3	SCr 5.2 mg/dl, urinalysis: RBC casts, proteinuria 2.9 g/24 h	NA	Methylprednisolone pulse 1 g for 3 days, plasmapheresis (indication: DAH), 3 doses of IVIG, 750 mg monthly CYC	Clinical improvement, SCr stable at 5.5 mg/dl
Mashinchi et al. [43]	21/F	RT-PCR positive	Known case of SLE. Abdominal pain, diarrhea, headache, fatigue, progressive dyspnea	Anti-PR3	Urinalysis: hematuria, RBC casts, proteinuria	Kidney — Class IV lupus nephritis with endocapillary proliferation with cellular crescents in glomeruli	Pulse methylprednisolone, CYC	Passed away after seizures, ARDS
Shakoor et al. [44]	78/F	2 doses of Pfizer-BioNTech vaccine	Nausea, vomiting diarrhea, fatigue	Anti-MPO	SCr 3.54 mg/dl. Urinalysis: 56 RBC/HPF, 13 WBC/HPF, 100 mg/dl protein, 1–2 granular casts/HPF	Kidney — pauci-immune crescentric necrotizing glomerulonephritis	Methylprednisolone 1 g/day for 3 days, followed by, prednisolone 1 mg/kg/day, rituximab	Clinical improvement with SCr 1.7 mg/dl at 1-month follow-up
Duran et al. [45]	26/M	RT-PCR positive	Fever, fatigue, cough	Anti-MPO	SCr 6.03 mg/dl. Urinalysis: active sediments, dysmorphic erythrocytes	Kidney — pauci-immune crescentic glomerulonephritis with IFTA	Pulse methylprednisolone 1 g for 3 days, hemodialysis, plasma exchange (DAH), CYC	Continued on hemodialysis
Duran et al. [45]	36/F	RT-PCR positive	Fever, cough, dyspnea, hearing loss	Anti-PR3	SCr 1.91 mg/dl	Kidney — pauci-immune crescentic glomerulonephritis	Pulse methylprednisolone 250 mg for 3 days, CYC	Clinical improvement, with SCr 1.41 mg/dl Hearing loss persisted

Table 3 (continued)

Author	Age/sex	SARS-C0V-2 infection/vaccine	Clinical features	Anti-MPO/anti-PR3	Renal involvement	Biopsy	Treatment	Outcome
Hakroush et al. [46]	79/M	2 doses of Pfizer-BioNTech COVID vaccine	Pain in the thighs with muscle weakness	Anti-MPO	SCr 1.38 mg/dl, CK 14,243 U/l. urinalysis: pyuria, hematuria, proteinuria > 18,000 mg/g creatinine	Kidney — severe ATN, pauci-immune crescentic glomerulonephritis with myoglobin casts	Pulse methylprednisolone 250 mg for 3 days, CYC (1 dose. Not repeated)	Kidney function improved, proteinuria 1603 mg/g creatinine, normal CK
Yadav et al. [47]	52/F	Johnson & Johnson adenoviral vector vaccine	Fever, arthritis, proximal weakness	Anti-MPO and anti-PR3	SCr 6.13 mg/dl. Urinalysis: hematuria, proteinuria	Kidney — necrotizing and crescentic pauci-immune glomerulonephritis	Methylprednisolone, CYC	Clinical improvement by 10 days
Hasbani et al. [48]	47/F	1st dose of Pfizer-BioNTech COVID mRNA vaccine	Generalized weakness, pedal edema, flank pain	Anti-MPO	SCr 2.91 mg/dl. Urinalysis: 40–50 RBC/HPF, 8–10 WBC/HPF	Kidney — crescentic pauci-immune glomerulonephritis	Pulse methylprednisolone 500 mg for 3 days, Azathioprine	Clinical improvement and normalization of creatinine at 3 months follow-up
Chang Kim et al. [49]	72/F	2 doses of Astra Zeneca and 3rd dose of Moderna vaccine	Fever, abdominal pain, anorexia	Anti-MPO	Urinalysis: hematuria 10–30 RBC/HPF, proteinuria	Kidney — pauci-immune glomerulonephritis	Methylprednisolone 500 mg, plasmapheresis, CYC	Normalization of creatinine and complete clinical improvement by 2 months
Sekar et al. [50]	52/M	2nd dose of Moderna vaccine	Headache, fatigue and weakness	Anti-PR3	SCr 8 mg/dl to 10.4 mg/dl. Urinalysis: microscopic hematuria, proteinuria	Kidney — crescentic pauci-immune glomerulonephritis	Rituximab (stopped due to infusion reaction), CYC, HD	Continued to require HD at 2 weeks follow-up
Al-Yafaei et al. [51]	62/F	Pfizer-BioNTech vaccine	Intermittent polyarthritis, hematemesis, progressive dyspnea. Diminished sensorium	Anti-PR3	SCr 3 mg/dl. Urinalysis: microscopic hematuria	NA CT brain — multi foci of hemorrhages, DAH	Pulse methylprednisolone, plasmapheresis, 4 doses of RTX, 2 doses of CYC	Pulmonary hemorrhage subsided, however no improvement in neurological function
Powell et al. [52]	12/F	SARS-CoV-2 IgG positive	Arthritis, cough, progressive dyspnea, hemoptysis	Anti-MPO	Urinalysis: hematuria	Kidney — pauci-immune necrotizing and crescentic glomerulonephritis BAL — diffuse alveolar hemorrhage	Pulse methylprednisolone, rituximab, CYC	Good clinical improvement

Table 4 Summary of cases of IgAV reported post-COVID and vaccine

Author	Age/sex	COVID infection or vaccination	Latent period	Clinical features	Renal involvement	Biopsy — skin/kidney	Treatment	Outcome
Sandhu et al. [62]	22/M	RT-PCR positive	With SARS-CoV-2 infection	Fever, abdominal pain, vomiting, arthritis — wrists and ankles, multiple discrete to confluent palpable purpura over both lower limbs, buttocks, trunk	Proteinuria 2 g/day	Skin — Leukocytoclastic vasculitis, DIF negative (delayed > 48 h duration) Kidney — focal necrotizing, mesangial, and focal endocapillary proliferative IgA nephropathy with mesangial granular deposits of IgA	1 mg/kg prednisolone for 10 days, tapered over 1 month. MMF	Resolved over 2 weeks
Jacobi et al. [63]	3/M	RT-PCR positive	With SARS-CoV-2 infection	Palpable purpura over lower limbs, abdominal pain and vomiting,	No	NA		Clinical improvement in 4 days
Allez et al. [64]	24/M	RT-PCR positive	1 week	Palpable purpura over both lower limbs, polyarthritis, abdominal pain	No	Skin biopsy — leukocytoclastic vasculitis, with neutrophil infiltration in the vessel walls and perivascular areas. IF — C3 and IgA deposits in dermal capillaries	Methylprednisolone 0.8 mg/kg, LMWH	Clinical improvement in 1 week
Sugita et al. [65]	67/F	Pfizer-BioNTech COVID-19 — 2nd dose, 1st dose 3 weeks prior	Same day	Palpable purpura on both legs, hips, upper limbs with subcutaneous edema, gross hematuria	Proteinuria 5.1 g/gCr, eGFR — 52.6 ml/min/1.72m^2	Skin biopsy — leukocytoclastic vasculitis; kidney biopsy — mesangial or endocapillary proliferation with necrotizing crescents in some glomeruli. IF — IgA and C3 deposits in the mesangium	Methylprednisolone 500 mg for 3 days, followed by 40 mg prednisolone, monthly IV CYC for 4 months, with a glucocorticoid taper to 10 mg PDN per day by 4 months	Reduction in proteinuria to 1 g/gCr after 4 pulses of IV CYC

Table 4 (continued)

Author	Age/sex	COVID infection or vaccination	Latent period	Clinical features	Renal involvement	Biopsy — skin/kidney	Treatment	Outcome
Li et al. [66]	30/M	RT-PCR positive	With the infection	Palpable purpura over both lower limbs, abdominal pain, diarrhea, bilateral wrist pain, frothy urine	Proteinuria, hematuria 11–20 RBC/HPF	Skin biopsy — leukocytoclastic vasculitis Kidney biopsy — focal crescentic and segmental necrotizing glomerulonephritis with endocapillary hypercellularity. IF — mesangial and peripheral wall staining for IgA with a score of 3 + Electron microscopy — subendothelial and mesangial immune deposits	40 mg PDN for 7 days, followed by a gradual taper	Microscopic hematuria persisted 6 weeks later
Suso et al. [67]	78/M	RT-PCR positive	3 weeks	Lower limb palpable purpura, wrist arthritis	Massive proteinuria — 10 g/day, hematuria with 60% dysmorphic RBCs	Skin biopsy — cutaneous leukocytoclastic vasculitis Kidney biopsy — segmental mesangial expansion with hypocellularity. IF — IgA granular deposition in the mesangium	Methylprednisolone pulse followed by oral steroids, rituximab	Purpura subsided, proteinuria persisted (6 g/day)
Alghoozi et al. [68]	4/M	RT-PCR positive	37 days	Maculopapular rash involving bilateral lower limbs and buttocks, ankle arthritis	No	NA	Paracetamol	Complete resolution of symptoms at 1-week follow-up
Ramdani et al. [69]	57/M	RT-PCR positive	1 week	Palpable purpura at both upper and lower limbs, abdominal pain, edema and painful ankle	Microscopic hematuria, proteinuria 2.7 g/24 h	Skin biopsy — IgA deposits in cutaneous vessels Kidney biopsy — mesangial IgA deposition with endocapillary proliferation	125 mg methylprednisolone for 3 days, followed by 1 mg/kg/day PDN with a slow taper over 2 months, angiotensin-receptor blocker	Normalization of creatinine and discontinuation of steroids at 2 months, with no further relapse

Table 4 (continued)

Author	Age/sex	COVID infection or vaccination	Latent period	Clinical features	Renal involvement	Biopsy — skin/kidney	Treatment	Outcome
Ramdani et al. [69]	41/F	RT-PCR positive	15 days	Palpable purpura over both lower limbs, elbow, right knee, and ankle arthritis	Microscopic hematuria, proteinuria 3.7 g/24 h	Kidney biopsy — endocapillary proliferation with glomerulonephritis and mesangial IgA deposition	20 mg/kg pulse methylprednisolone for 5 days, followed by 1 mg/kg/day of oral PDN tapered over 6 months	Complete resolution at 7 months follow-up
Ramdani et al. [69]	24/F	RT-PCR	27 days	Palpable purpura of both upper limbs and lower limbs and ankle arthralgia		Skin biopsy — cutaneous leukocytoclastic vasculitis with IgA deposits in cutaneous vessels	No specific treatment	Complete resolution, was self-limiting

CYC, cyclophosphamide; *DIF*, direct immunofluorescence; *HPF*, high power field, *LMWH*, low-molecular weight heparin; *MMF*, mycophenolate mofetil; *PDN*, prednisolone; *RT-PCR*, real-time polymerase chain reaction; *S.Cr*, serum creatinine

following a trigger from SARS-CoV-2 infection or its vaccine. The only evidence available is the outcome of COVID-19 in BD and that varied geographically. A large cohort of 1047 patients from Turkey reported a nearly doubled incidence of COVID-19 in patients with BD as compared to the general population [70]. These findings were mirrored in studies from Italy, Spain, and the Netherlands, who also reported an increased incidence of COVID-19 in these patients, though there was no evidence of higher mortality [71–73]. However, an Iranian cohort reported otherwise; in a follow-up of 59 BD patients, they observed that there was no increase in incidence or mortality [74].

We did not find confirmed cases of BD reported after COVID-19. There are some case reports of BD-like disease after vaccination [75, 76]. Similarly, there is a report of a major flare of BD post mRNA vaccination. An isolated report from India described that painful stomatitis and genital ulcers with papulopustular lesions resembling acne developed following the ChAdOx1 nCoV-19 vaccine [77]. However, owing to the absence of typical features of vasculitis, a negative pathergy, and sparing of the eye, the diagnosis of BD was unlikely [78]. The apparent rarity of BD post- COVID or post-COVID vaccination is contrary to our expectations. After understanding the pathophysiology of BD, it seems natural that COVID-19, with its predilection for thrombosis and neutrophil involvement, may also predispose to such pathology [79]. Unlike in BD, there is little evidence of the involvement of venules and veins in COVID-19. Also, the thrombosis in BD responds to immunosuppressants rather than heparin that has a mortality benefit in COVID-19 [6]. Thus, it appears that BD and COVID-19 may have different underlying pathophysiology and hence the incidence of post-COVID-19 BD is rare.

Conclusion

Both SARS-CoV-2 and COVID-19 vaccines have the potential to induce systemic vasculitis resembling phenotypes of primary vasculitides. IgA vasculitis is the most prevalent form of vasculitis reported after either COVID-19 infection or vaccination. The virus-induced vasculitis seems to have a better prognosis than de novo systemic vasculitis, with a favorable response to systemic corticosteroids with or without immunosuppression. However, the available data is mostly based on anecdotal reports, case series, or cross-sectional studies, and long-term follow-up is required before downplaying the severity of vasculitis following SARS-CoV-2 infection. This necessitates a concerted global effort to collect and monitor the cases using a multi-omics approach based on the principles of predictive medicine.

The COVID vaccines have also been implicated as a possible trigger for systemic vasculitis, with cutaneous leukocytoclastic vasculitis and IgAV being the most frequent. However, these symptoms were transient and responded promptly to glucocorticoids with no lasting damage. Also, since the evidence is again only from case reports, establishing a causal link with the vaccine is not always straightforward.

Given that the vasculitis post-COVID-19 affects all vessels indiscriminately, a proposition to classify it under the Chapel-Hill Consensus Classification of vasculitis as "vasculitis associated with a specific virus" seems reasonable. Long-term follow-up data of these patients is essential to ascertain the course of the disease, prognosis, and the necessity, or not for stronger immunosuppression.

In conclusion, physicians must be vigilant to distinguish cases of vasculitis in the context of COVID-19. Steroids are central to the treatment and most reported cases have seen benefit with 0.8 to 1 mg/kg/day of prednisolone. The requirement for pulse methylprednisolone, additional cytotoxic, and immunosuppressive therapy should be determined on an individual basis, depending on major organ involvement and the rapidity with which the disease progresses. And finally, patients receiving B-cell-depleting therapy, mostly those with pre-existing AAV, have a diminished immunogenic response to the vaccine and they may therefore be more susceptible to developing a more severe phenotype of COVID-19.

Author contribution All the authors substantially contributed to the drafting and revision of the manuscript. They take full responsibility for the integrity of all aspects of work.

Declarations

Disclosures None.

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Rheumatology International
https://doi.org/10.1007/s00296-024-05712-3

CASES WITH A MESSAGE

SARS-CoV-2 as a trigger of IgA vasculitis: a clinical case and literature review

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Received: 18 July 2024 / Accepted: 21 August 2024

Abstract

Coronavirus Disease 2019 (COVID-19), caused by SARS-CoV-2, has negatively affected global health. COVID-19 has been associated with a variety of autoimmune and inflammatory disorders, complicating its respiratory manifestations. SARS-CoV-2 triggers inflammatory reactions which may involve multiple organs and systems. The proof for IgA involvement in the immune reactions to coronavirus infection is growing, particularly in the case of IgA immune complex deposition diseases such as IgA vasculitis (IgAV) and IgA nephropathy.

This report presents a case of IgAV caused by SARS-CoV-2 in a 53-year-old man. His symptoms included papillomatous, bright red rashes, urticaria throughout the body, aphthous stomatitis, pain in all joints and muscles, weakness, malaise, abdominal pain, face swelling, and arterial hypertension (160/100 mmHg). He received intravenous methylprednisolone (250 mg) and then oral methylprednisolone (16 mg) treatment, which improved his condition. This improvement included the disappearance of abdominal and joint pain and skin rashes.

This article also provides an overview of published cases of IgAV after SARS-CoV-2. It may alert rheumatologists and allied specialists of clinical features of IgAV and guide them how to diagnose and treat this disease.

Keywords IgA vasculitis · Henoch-Schonlein purpura · Vasculitis · COVID-19 · Coronavirus infection · SARS-CoV-2

Introduction

Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, is a global health issue, with millions of recorded fatalities [1]. Since the start of the COVID-19 pandemic, various autoimmune and inflammatory conditions associated with COVID-19 have been reported, including systemic lupus erythematosus, systemic sclerosis, autoimmune cytopenia, cutaneous vasculitis, and Guillain-Barre syndrome [2].

IgA vasculitis (IgAV) is caused by the accumulation of IgA immune complexes in the skin and other organs, resulting in small-vessel vasculitis. It can be triggered by various microorganisms [3]. IgAV, also known as Henoch-Schonlein Purpura (HSP), is a type of small-vessel vasculitis that commonly develops following viral infections. It frequently appears with petechial rash [4].

The incidence rate of IgAV varies widely, with the average annual incidence rate per 100,000 persons being as follows: Croatia − 6.8, Great Britain − 6.21 and 20.4, Taiwan − 12.9, the Netherlands − 6.1, Sweden − 17.5, Korea-55.9 [5–7]. Ethnic disparities have been explored in the context of IgAV; the disease is more prevalent in children of Caucasian or Asian origin than in Black juveniles [8]. Different clinical forms of IgAV have been described. Leukocytoclastic (LCV) IgAV and vasculitis resembling Kawasaki disease have been frequently associated with COVID-19 [9].

IgAV symptoms consist of elevated purplish rash, abdominal discomfort with or without internal bleeding, joint pain, visible blood in the urine, and severe proteinuria [10].

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Published online: 09 September 2024

Distinct immune inflammatory reactions are known in the context of COVID-19, manifesting with both acute (within 14 days of the infection) and chronic vasculitides [11]. The exact cause of SARS-CoV-2-induced IgAV is not fully understood. Nevertheless, it is believed that COVID-19 may overly activate the immune system, trigger an exaggerated response of neutrophil-associated cytokines and augment the accumulation of immune complexes in tissues [12]. Cutaneous vasculitis may evolve during or after the SARS-CoV-2 infection, affecting dermal and hypodermal vessels. Medications, vaccines, and infectious diseases can trigger cutaneous vasculitis. The typical cutaneous vasculitides are cutaneous small-vessel vasculitis, urticarial vasculitis, IgAV (skin-limited), and lymphocytic vasculitis [13–15].

Herein we present a case of IgAV triggered by SARS-CoV-2 infection. We also analyze similar published cases pointing to a hypothesis that SARS-CoV-2 triggers IgAV.

Clinical case presentation

A 53-year-old man was admitted to hospital for urgent care due to symptoms of SARS-CoV-2 infection. These symptoms included difficulty breathing, cough, loss of taste and smell, significant fatigue, and subfebrile fever (37.5 °C). A nasopharyngeal swab was taken for SARS-CoV-2, and the result was positive.

On physical examination, the patient was conscious. The skin was pale, without rashes. The lymph nodes were not enlarged. In the oropharynx, the mucous membrane of the posterior wall was hyperemic; the tonsils were not enlarged.

Laboratory and instrumental tests

The PCR test was positive, and computed tomography (CT) revealed polysegmental pneumatic infiltration in both lungs (lung damage of approximately 40%). Control CT identified multifocal lung lesions, characterizing the incompletely resolved stage of SARS-CoV-2 infection.

After two weeks, the patient was discharged in compliance with the requirements of quarantine measures. Following the discharge from the hospital, the patient experienced insomnia, requiring treatment by tricyclic antidepressants (amitriptyline).

After four months, the patient noticed papillomatous, bright red rashes, urticaria throughout the body, aphthous stomatitis, pain in all joints and muscles, arthritis (swelling of the left knee joint), abdominal pain, weakness, malaise, face swelling, and an increase in blood pressure to 160/100 mmHg.

The patient experienced these symptoms for three weeks before seeking treatment by an allergist. The allergist prescribed glucocorticosteroids (dexamethasone) and complex agents (sodium thiosulfate), but the patient did not notice any improvement. Afterward, the patient was referred to rheumatology center for diagnosis. The patient's antinuclear factor (ANF) and ANCA were positive, suggesting a potential autoimmune component of the patient's condition. The patient had no history of hepatitis B, pulmonary tuberculosis, skin or venereal diseases. He did not undergo hemotransfusions, injuries, or surgical interventions. The patient had an allergic history (allergic reaction to diphenhydramine).

Immunoblot ANF 1/80; ANCA 1/20; CRP positive; antistreptolysin O antibody (ASLO) positive. HIV and hepatitis B and C tests were negative. After investigations, IgAV (HSP, skin-joint form, high degree of activity) triggered by COVID-19 was suspected based on the complaints and anamnesis. Skin biopsy findings were also consistent with IgAV and supported the clinical diagnosis.

Laboratory tests during treatment

Blood tests: hemoglobin 13 g/dL, leukocytes 7.9×10^9/L, granulocytes 62%, platelets 153×10^9/L, erythrocytes 4.4×10^{12}/L; ESR 5 mm/h. Urinalysis: bilirubin 0 μmol/L, glucose 0 mmol/L, ketone bodies 0 mmol/L, leukocytes 2 leukocytes per μL, relative density of urine 1010, pH 6, urobilinogen 0.2 μmol/L, 0 erythrocytes per mL, protein in urine 0 g/L.

The general biochemical blood tests: total bilirubin 4.5 μmol/L, serum glucose 4.2 mmol/L, ALT 101 IU/L, AST 28 IU/L, serum urea 8.1 mmol/L, creatinine 93 μmol/L, CRP 0.3 mg/L. RF 7.7 IU/L.

Treatment

The treatment included the following: non-steroidal anti-inflammatory drugs (NSAIDs) (meloxicam), metronidazole, glucocorticosteroids (methylprednisolone 250 mg, IV administration), anticoagulants (5 ml, 5000 IU/ml solution), and azithromycin 500 mg/daily.

The response to the treatment was positive, with a regression of the rash. (hyperpigmentation in the rash sites, and no new rash elements). Arthralgia and muscular pain diminished, weakness showed improvement, abdominal pain decreased, and blood pressure was under control. In addition, the swelling in the left knee decreased. It was recommended that methylprednisolone 16 mg/daily be taken for one month, followed by a dose reduction according to the scheme under blood sugar control, as well as dabigatran etexilate 110 mg and omeprazole 20 mg while

taking methylprednisolone. The patient was discharged with improvement.

Search strategy and case selection

A comprehensive search was conducted for articles describing cases of IgAV after COVID-19 through Medline/PubMed, Scopus, and the Directory of Open Access Journals (DOAJ). The timeline spanned from December 1st, 2019 to June 1st, 2024. The following keywords were employed: IgA vasculitis, Henoch–Schonlein purpura, Vasculitis, COVID-19, and SARS-CoV-2. Only English articles were analyzed. The search covered patients aged above 18. Reports of IgAV after COVID-19 vaccination were not analyzed. Cases without complete clinical descriptions were excluded. Cases in which the diagnosis was ambiguous or COVID-19 was not explicitly reported were also excluded.

Literature review

The current literature on the development and exacerbation of vasculitis triggered by COVID-19 is mostly represented by case reports. Patients with established autoimmune diseases may experience vasculitis following coronavirus infection [16].

One proposed mechanism of COVID-19-induced IgAV is the virus's direct damaging effect on blood vessels, followed by the formation of immune complexes and localized inflammation. The viral induction of systemic inflammation may be another mechanism that leads to the development of IgAV. There have been reports of IgAV after COVID-19 vaccination, suggesting a potential link to the spike protein used in certain vaccines. Nevertheless, no exact mechanism exists to explain the connection between coronavirus infection and IgAV [4, 17]. IgAV may develop in individuals recovered from coronavirus infection, and related instances have been observed following vaccinations [12].

In Table 1, several cases of IgAV with kidney involvement were analyzed. IgAV with notable renal impact is an infrequent outcome of SARS-CoV-2 infection. Diagnosis of renal involvement in individuals with SARS-CoV-2 is likely to predict poor outcome. The development of glomerulonephritis confound the treatment tactics [18]. The virus may affect almost all organ systems, manifesting with skin rashes and renal, cardiac, and other signs [4, 19].

In a previous systematic overview of 13 cases of IgAV after COVID-19, renal involvement was diagnosed in 7 subjects [20]. The results of that overview, coupled with other studies in the field, suggest that skin, joint, and kidney involvement are common in IgAV after COVID-19 and that glucocorticosteroid use often exerts beneficial effects [20, 21].

The coronavirus infection is constantly changing, and healthcare professionals should be aware of diverse clinical presentations of the disease. Cutaneous signs in IgAV following COVID-19 include measles-like, chilblain-like hives, pimples and scales, flat red patches, blisters, and net-like purple discoloration [22, 23].

Selecting the appropriate test for coronavirus infection diagnosis requires careful evaluation of the test purpose and available resources and consideration of the test's accuracy, accessibility, cost-effectiveness, and speed of results. Three types of diagnostic tests effectively support patient management and detection of coronavirus infection. These tests include PCR tests that detect viral RNA, identify viral proteins (such as nucleocapsid or spike proteins), and serology tests that determine the antibodies the host produces following infection/vaccination [24]. The most reliable method for diagnosing coronavirus infection is RT-PCR [25].

Ansari et al. utilized droplet digital polymerase chain reaction (ddPCR) to confirm following a negative nasal swab PCR [22]. This method showed greater sensitivity than standard nasal swab PCR in identifying samples with low SARS-CoV-2 viral load, potentially leading to a reduced rate of inaccurate results and a more effective SARS-CoV-2 testing and diagnosis process.

According to Valero et al., patients with IgAV after COVID-19 may need immunosuppressive therapy [16]. Tudorache et al. stated that treatment for non-complicated cases of IgAV usually involves NSAIDs to decrease inflammation and alleviate pain [26]. The use of glucocorticosteroids has been demonstrated to reduce the duration of abdominal pain symptoms [27]. However, it does not impact the progression of the disease in juvenile patients. If there is concern about urinary system participation, it is recommended to consider using angiotensin-converting enzyme inhibitors [28]. The treatment and medication dosage are determined on a case-by-case basis, considering the seriousness of the disease, any accompanying conditions, and other relevant factors.

Table 1 presents data on IgAV after COVID-19 [4, 16, 18, 21, 22, 29–35].

Discussion

IgAV occurs mainly in children as leukocytoclastic vasculitis with systemic immune reactions. It is characterized by palpable purpura without thrombocytopenia, joint pain, and abdominal discomfort [36, 37]. The exact mechanism of IgAV has yet to be discovered. IgAV is linked to past bacterial and viral infections, vaccinations, food allergies, and medication use [18]. Upper respiratory tract infections can trigger the disease, marked by an immune response

Table 1 IgA vasculitis developed after COVID-19

Author	Sex	Age	Anamnesis	Previously diagnosed IgAV	COVID-19 status	Time from COVID-19 to the onset of IgAV	Clinical manifestations	Treatment	Outcome
Valero et al. [16]	Male	27	Unremarkable	HSP 3 years earlier (remission)	Positive PCR	One month	Leukocytoclastic vasculitis and palpable purpura	Prednisone Azathioprine	Improvement of the purpuric lesions and kidney function
Allez et al. [29]	Male	24	Crohn's disease	-	Positive PCR (asymptomatic)	At the same time	Leukocytoclastic vasculitis, discomfort in the abdomen, and arthritis.	Methylprednisolone	Discharged on the 7th day
Yousef Salem et al. [4]	Female	21	Unremarkable	-	Positive PCR	At the same time	Petechial rash of both extremities. Biopsy: a slight perivascular neutrophil infiltrate in the superficial dermis with extravasation erythrocytes	Prednisone Azathioprine	Unknown
Nicholas L Li et al. [18]	Male	30	Unremarkable	-	Positive NAATs	At the same time	Flare of the IgAV (purpuric rash, arthralgia, and abdominal pain) IgA nephropathy Biopsy-proven leukocytoclastic vasculitis	Prednisone	Improvement
Suso et al. [30]	Male	78	Alcohol intake, high blood pressure, mild narrowing of the aortic valve, and previous treatment for bladder cancer (in remission)	-	Bilateral pneumonia and positive PCR	Three weeks	Purpura of the lower extremities, arthritis, and leukocytoclastic vasculitis	Prednisone	Discharged with an improvement
Valero et al. [16]	Female	62	Unremarkable	HSP 4 years earlier (remission)	Positive test for IgG COVID-19 antibodies	Three months	Palpable purpura IgA nephropathy	Methylprednisolone-Rituximab Prednisone	Improvement
Barbetta et al. [31]	Male	62	Unremarkable	-	Bilateral interstitial pneumonia and positive PCR	Ten days	Purpuric lesions with raised papules on the lower extremities with renal and gastrointestinal involvement	Methylprednisolone Mycophenolate mofetil	Improvement
Sandhu et al. [32]	Male	22	Unremarkable	-	Positive PCR	Two days	Palpable purpura IgA nephropathy	Dexamethasone	Improvement
Jedlowski et al. [33]	Male	70	Unremarkable	-	Positive PCR	Seven days	Flare of the IgAV (palpable purpura, arthralgia, abdominal pain, diarrhea, and a purpuric rash on the bilateral lower extremities), and leukocytoclastic vasculitis	Methylprednisolone Prednisone	Significant improvement
Suszek et al. [21]	Female	58	Unremarkable	-	Pneumonia and positive PCR	At the same time	Flare of the IgAV (palpable purpura, arthralgia, myalgia, aphthous stomatitis, and swelling on the face)	Methylprednisolone	Significant improvement
Alwafi et al. [34]	Female	41	Unremarkable	-	Positive PCR	Two weeks	Palpable purpura and arthralgia	Methylprednisolone Hydroxychloroquine	Significant improvement

Table 1 (continued)

Author	Sex	Age	Anamnesis	Previously diagnosed IgAV	COVID-19 status	Time from COVID-19 to the onset of IgAV	Clinical manifestations	Treatment	Outcome
Chang et al. [35]	Female	23	Unremarkable	-	Positive PCR	One week	Palpable purpura, arthralgia, abdominal pain, and leukocytoclastic vasculitis	Methylprednisolone Prednisone	Complete disappearance of the purple rash, joint and abdominal pain
Ansari et al. [22]	Male	50	Gout	-	SARS-CoV-2 tissue testing on a biopsy (ddPCR)	At the same time	Palpable purpura and bilateral ankle swelling	Prednisone Topical corticosteroids	Resolution
Present case	Male	53	Unremarkable	-	Polysegmental pneumatic infiltration of both lungs (lung damage by 40%) and positive PCR	Five months	Palpable purpura, arthritis, and swelling of the left knee joint	Rheumoxicam Methylprednisolone	Discharged on the 14th day with an improvement

COVID-19: Coronavirus disease 2019; HSP: Henoch-Schonlein purpura; IgAV: IgA vasculitis; PCR: Polymerase chain reaction; NAAT: Nucleic acid amplification test

involving IgA reacting to antigens. IgAV is caused by the bu, such as leukocytoclastic vasculitis, ildup of IgA immune complexes in the skin and other organs. Different microorganisms, including viruses, can initiate the process [3].

In adults, joint damage linked to IgAV was documented in approximately 60% of instances [38–40]. Myalgia manifests without notable alterations in creatinine kinase levels [41]. Gastrointestinal involvement is prevalent, manifesting in around two-thirds of cases. The predominant gastrointestinal symptoms in adults are abdominal pain (76.7%), hematochezia (30%), and nausea and vomiting (16.2%) [42]. Adults are more prone to renal disease, with about 76.2% of patients experiencing proteinuria and haematuria [42–44].

COVID-19 can stimulate the immune system response through IgA, accumulating the IgA immune complex in various organs and blood vessels, causing tissue damage [9]. The proof for IgA's involvement in the immune reaction to coronavirus infection is growing, leading to a rise in IgA immune complex deposition diseases such as IgAV and IgA nephropathy [45, 46]. COVID-19 vaccines may act as triggers in systemic vasculitides, such as cutaneous leukocytoclastic vasculitis and IgAV [47].

We overviewed 14 cases (with our own case, 5 females and 9 males) of first-time IgAV in patients with COVID-19, presumably associated with this infection. When examining the disparities between male and female subjects in the available literature, it appears that males have a higher susceptibility than females [48, 49].

In six cases, the disease started at the same time as IgAV, while in the remaining 8 cases, vasculitis symptoms developed after several days or months. This finding indicates that IgAV may coexist with COVID-19 and that the clinical picture may also present at post-infection follow-up. Although we cannot entirely rule out the coincidental association of IgAV, symptoms, positive PCR test for COVID-19, and temporary associations between IgAV and COVID-19 suggest that SARS-CoV-2 may be the cause of IgAV. Also, according to the literature, the most common rheumatic symptoms associated with COVID-19 are vasculitis and arthritis [50].

In a multicenter cohort study on 1988 IgAV patients, a significant impact of the COVID-19 pandemic on IgAV features was noticed, with a reduction in IgAV occurrence rates among children [49]. A decrease in IgAV cases during the COVID-19 pandemic was noted in Türkiye [51], similar to our previous research in Kazakhstan examining the impact of COVID-19 on systemic vasculitis patients [52]. The decrease in IgAV cases amid the COVID-19 pandemic can be the result of low referrals of patients to specialist centers [51, 52].

As our understanding of the IgAV link to coronavirus infection is still evolving, any patient suffering and recovering from COVID-19 with skin rashes or joint pain must seek

immediate medical attention. Early diagnosis and treatment of IgAV is crucial for avoiding long-term complications [34].

Patients with IgAV are subject to diverse treatment tactics, depending on severity of the condition and presence of systemic manifestations [53]. The standard carefor IgAV involves managing symptoms and providing targeted treatment to reduce potential difficulties [35].

In our study, the majority of overviewed cases were treated with glucocorticosteroids in addition to antibiotics, NSAIDs, biologic agents, and antihypertensives. Positive outcomes were recorded in most cases. The latter is in line with the concept of IgAV as a self-limiting condition. However, it is unclear whether these positive outcomes were due to self-limiting nature of IgAV or usefulness of glucocorticosteroids.

The current study has several limitations. Although some cases of IgAV after COVID-19 have been documented in the literature, the overall number of cases remains limited. As a result, the generalizability of the current study is restricted. Second, the paucity of long-term follow-up data limits our knowledge of the long-term effects of SARS-CoV-2-induced IgAV. Although temporal association between SARS-CoV-2 infection and IgAV start was recorded, establishing a direct causative link is challenging due to the multifaceted nature of autoimmune disorders.

Conclusion

The overviewed cases suggest a possible connection between COVID-19 and IgAV. SARS-CoV-2 may trigger IgAV. IgAV may develop during and after coronavirus infection (within few days - several months). Healthcare professionals should be aware of the potential association between COVID-19 and IgAV to provide timely and effective care to affected patients. Prompt detection and treatment with glucocorticosteroids result in a quick recovery. Further research with a larger case series is warranted to clarify the precise role of SARS-CoV-2 in the development of IgAV.

Author contributions AA and MY designed the study. AA, MY, and BFK reviewed the literature and collected the data. AA, MY, and BFK analyzed the data. AA, MY, and BFK interpreted the data analyses. AA, MY, and BFK drafted and reviewed the study critically for important intellectual content. AA, MY, and BFK prepared the table. AA, MY, and BFK approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Funding None.

Declarations

Informed consent Written informed consent was obtained from our patient.

Conflict of interest None declared.

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Rheumatology International
https://doi.org/10.1007/s00296-024-05582-9

Rheumatology
INTERNATIONAL

REVIEW

Diagnostic delays in systemic vasculitides

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Received: 2 January 2024 / Accepted: 12 March 2024

Abstract
Systemic vasculitides are among the less common disorders encountered in routine rheumatology practice. The low incidence and heterogeneous presentation at onset can potentially lead to delayed diagnosis. Not recognizing these in the early phase may prove detrimental, as some vasculitis may progress to a catastrophic course with major morbidity or mortality. The causes of diagnostic delay may vary among different types of vasculitis and may also be disease-, patient-, or physician-related. Disease-related factors include the myriad presentations with diverse and non-specific symptoms, mimicking other conditions like infections. In addition, some forms have prolonged prodromal phases before evident organ damage. Limited awareness among healthcare professionals, particularly outside rheumatology, and a lack of readily available diagnostic tools contribute to missed diagnoses. Delays in seeking care due to non-specific symptoms or lack of access to specialist care can worsen outcomes. The economic burden also increases with delayed diagnosis and damage accrual when the disease remains unrecognized or untreated for prolonged periods. Although the causes of vasculitis are numerous, including secondary causes, in this review, we focus on diagnostic delays in primary vasculitides and suggest potential steps to identify and treat these diseases early. These include educating both healthcare professionals and the public about the signs and symptoms of vasculitis; expanding the rheumatology workforce and facilitating timely referrals; implementing readily available and reliable tests for early detection; and streamlining care and diagnostic pathways. Such measures have the potential to improve the overall outcomes of the disease, with prolonged remission, minimal damage accrual, and improved quality of life.

Keywords Vasculitis · Delayed diagnoses · Anti-neutrophil cytoplasmic antibody-associated vasculitis · Takayasu arteritis · Giant cell arteritis

Introduction

Autoimmune rheumatic diseases (AIRDs) are a heterogeneous group of diseases in which the onset of clinical manifestations is often preceded by a prolonged subclinical or preclinical phase of autoimmunity [1]. This may be followed by a prodromal phase with mild symptoms that often lasts for years. Eventually, with the onset of frank clinical signs, there exists a "therapeutic window of opportunity" that is the potential target to achieve maximum benefit to treatment with the least long-term damage accrual, translating to better outcomes [2–4]. However, systemic vasculitides are usually different. They can present with an acute fulminant presentation like rapidly progressive renal failure or indolently like just very slow interstitial lung disease with arthralgia and sinusitis as in the case of MPO (myeloperoxidase) vasculitis.

Among the most serious and potentially catastrophic diseases in the rheumatological spectrum, the vasculitides may present with a myriad of tessellations. Major organ manifestations of systemic vasculitides may be preceded by a prolonged prodromal phase that may be missed until the patient presents with symptoms of end-organ damage. Moreover, the increasing costs of treatment are directly proportional to diagnostic delays in the vasculitis [5, 6].

The period from the onset of symptoms to the confirmation of diagnosis or the initiation of definitive treatment is the most accepted definition of diagnostic delay. Multiple factors contribute to a diagnostic delay in vasculitis, including patient-related factors, variable disease presentations, and physician-related factors [3, 7]. The overall diagnostic delay in all AIRDs is estimated to be 30 weeks, which is the median time from the onset of symptoms to the first contact with a rheumatologist [3]. However, the time to actual diagnosis by a rheumatologist may vary depending on demographics and access to healthcare.

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Published online: 08 April 2024

After much deliberation to describe and classify these diseases, the Chapel Hill consensus in 1994 proposed the nomenclature and definitions for the well-recognized clinical and pathological types of vasculitis based on the type of vessel involved and was revised in 2012, and this has been adopted worldwide since [8, 9]. Vasculitis can also occur secondary to connective tissue diseases such as systemic lupus erythematosus (SLE), primary Sjogren's syndrome, or infections such as hepatitis B and C, human immunodeficiency virus (HIV), and tuberculosis [10]. However, in this review, we have restricted our discussion to diagnostic delays in primary systemic vasculitides classified under the revised Chapel Hill consensus [9].

A delay in diagnosis and initiation of treatment is associated with poorer outcomes and fewer chances of drug-free remission [11]. One caveat here could be the dilemma of obtaining a tissue for biopsy and that the treatment may alter the histopathological picture. However, it has been established beyond reasonable doubt that a few days of treatment would not significantly change the diagnostic yield of a biopsy, and this delay in obtaining tissue may prove detrimental [12]. Beyond a delay in treatment initiation and the threat of impending organ damage, the healthcare costs of not diagnosing systemic vasculitis on time also become steeper as there is a potential threat of long-term damage accrual and recurrent hospitalizations [13, 14].

In this review, we aimed to analyze the possible reasons for the delay in the diagnosis of systemic vasculitis and its outcomes. We also discuss how health professionals encountering patients with vasculitis can minimize delays and initiate timely treatment.

Search strategy

We conducted a thorough search of PubMed/MEDLINE, Scopus, and Directory of Open Access Journals (DOAJ) using the keywords and medical search heading (MeSH) terms "systemic vasculitis", "vasculitis, ANCA", "Wegener's granulomatosis", "Churg-Strauss disease", "granulomatosis with polyangiitis", "microscopic polyangiitis", "eosinophilic granulomatosis with polyangiitis", "polyarteritis nodosa", "Kawasaki disease", "Takayasu arteritis", "giant cell arteritis", "Behcet syndrome", "Delayed Diagnoses" and "Diagnosis Delay", "Diagnosis, Delayed" in various combinations. Though the terms "Wegener's" and "Churg-Strauss" disease are obsolete, they were used to retrieve the articles published before 2011. Only articles dealing with systemic vasculitis as classified under the revised Chapel Hill Consensus Conference (CHCC) definitions, and exploring delays in diagnosis, were included [9]. In addition, we considered articles that were cross-referenced from the selected articles if relevant. We excluded conference abstracts, case reports, and articles published in languages other than English. The final manuscript was drafted following the recommendations for narrative review [15].

Factors associated with a diagnostic delay

The causes of diagnostic delay as mentioned in the literature are multifactorial but can be apportioned into factors related to the disease, the patient, or the physician. A global survey has shown that the factors contributing to a delay in diagnosis are heterogeneous and vary depending on the awareness of physicians regarding the definitions and classification of vasculitides, demographics, type of vasculitis, and access to healthcare or specialist rheumatologists [16]. Table 1 summarizes the findings of various studies looking at diagnostic delays in the management of systemic vasculitides.

Another factor that contributes to the delay or possible ambiguity in recognizing cases of systemic vasculitis is that they often mimic infection. The classical illustration is the COVID-19 pandemic when acute SARS-CoV-2 infection mimicked systemic vasculitis [46, 47].

Physician factors

Considering the low rheumatologist-to-patient ratio worldwide, including in most developed countries, the probability of a patient with systemic vasculitis presenting to a rheumatologist at onset is low. Moreover, different countries have different referral systems, which makes access to specialist care difficult to obtain unless there is proper awareness at the ground level [48]. As expected, patients presenting to rheumatologists, followed by internists, had the shortest diagnostic delay and time to initiation of induction therapy [26]. A common reason for delay in developing countries or physically remote areas in developed countries is the relative unavailability of diagnostic facilities such as temporal artery ultrasound, computerized tomography, magnetic resonance imaging, or positron emission tomography scan, which are of particular importance in large-vessel vasculitis, such as Takayasu arteritis (TAK) and GCA [49, 50].

Diagnostic errors also contribute to diagnostic delay in a minority of cases, especially AAV [51]. Patients with GPA tend to be misdiagnosed with infections such as tuberculosis [52, 53], mucocutaneous leishmaniasis [54], and malignancies such as myofibroblast tumors [55]. In addition, there may be some overlap in clinical features that can lead to misdiagnosis with another AIRD. For instance, before the advent of widespread testing for ANCA, elderly patients presenting with a predominant arthritis phenotype were diagnosed with polymyalgia rheumatica until the onset of glomerulonephritis, after which AAV was recognized. This results in a significant delay in the recognition and institution

Table 1 Summary of studies exploring the diagnostic delays in vasculitis

References	Type of study	Type of vasculitis	Number of patients	Causes of the diagnostic delay	Duration of delay
Poulton et al. [17]	Population-based case–control study	AAV	127	Absence of renal involvement at presentation may contribute to delay	Did not describe the duration of delay
Takala et al. [18]	Retrospective	GPA	489	Unavailability of ANCA tests during the first 5 years	17 months (1981) to 4 months (2000)
Yacyshyn et al. [19]	Online survey	GPA	912	An online survey that only assessed delay. Readers may infer delay due to predominant sinus symptoms and greatly varied clinical features at the onset	Variable (1 year in 36.4%; $n=912$)
Taimen et al. [20]	Retrospective	All primary systemic vasculitis, (excluded Goodpasture syndrome)	317	Assessed delay and costs incurred and not the cause for delay	LVV—median 5 days (IQR 13) AAV—median 22.5 days (IQR 38)
Sreih et al. [21]	Qualitative and quantitative survey	All primary systemic vasculitis	456	Unemployment, time to travel to medical center >1 h, initial misdiagnosis, delays in seeing a specialist	Median 7 months
Prior et al. [22]	Systematic review and meta-analysis	GCA	2474	Delay longer in non-cranial GCA (mean 17.6 weeks with 95% CI 9.7–25.5)	Mean 9 weeks (95% CI 6.5–11.4)
Popescu et al. [23]	Cross-sectional	AAV	26	Did not describe the causes of delay	Mean 2 years
Gudbrandsson et al. [24]	Population-based cohort	TAK	97	Limited access to imaging	63 months in cases diagnosed up to 1999; 14.5 months in those diagnosed from 2000 to 2012; 8 months (2010–2012)
Skaug et al. [25]	Retrospective	GCA	257	Longer delay in non-cranial GCA owing to the absence of typical symptoms	Median 82 days (non-cranial), 40 days (cranial)
Dirikgil et al. [26]	Retrospective	AAV	230	Non-generalized disease (22 days vs. 9 days in generalized disease) and ENT symptoms at presentation. Diagnosis by ENT specialist was delayed (57 days)	Median 13 days (IQR 2–49)
Sahin et al. [27]	Retrospective	Childhood-onset TAK	16	Angiographic extent of disease	2.5 months (IQR 0.9–9.6)
Thakare et al. [28]	Ambispective cohort	TAK	215	Did not report on the causes of delay	1.5 years (IQR 0.42–5)
Tomelleri et al. [29]	Retrospective	TAK	117	Not studied	92.9 ± 80.7 months in men, 63.03 ± 85.63 months in females

Table 1 (continued)

References	Type of study	Type of vasculitis	Number of patients	Causes of the diagnostic delay	Duration of delay
Misra et al. [30]	Retrospective	Childhood-onset TAK	29	Non-specific symptoms, claudication uncommon	1 year (IQR 0.42–2)
Clemente et al. [31]	Retrospective	Childhood-onset TAK vs. TAK in adolescents	71 (36 children, 35 adolescents)	Non-specific symptoms at presentation	1.2 years
Vanoli et al. [32]	Retrospective and prospective	TAK	104	Non-specific symptoms and signs at presentation	Average 46 months; median 15.5 months (IQR 0–365)
Goel et al. [33]	Retrospective	Childhood-onset TAK	40	Clinical features of TAK mimicking other conditions like suspected tuberculosis, PUO, meningitis, CVA, hypertensive encephalopathy, co-existing ulcerative colitis	11.3 months (IQR 1–60)
Heras-Recuero et al. [34]	Retrospective	LVV, mostly GCA	80 (GCA—64)	Extracranial GCA	Median 12 weeks (IQR 4–18)
Sriskandarajah et al. [35]	Prospective observational	AAV with glomerulonephritis	455	Reported that delays improved with better availability of ANCA testing	Not designed to test
Vinit et al. [36]	Retrospective	EGPA	31	Initial paucivisceral presentation leads to delay in diagnosis	Mean 61 months; median 36 months (IQR NA)
Huang et al. [37]	Retrospective	AAV	730	Non-specific symptoms in the prodromal phase like fatigue, fever, arthralgia	Not designed to evaluate delay, but to estimate costs associated with delay
Van Nieuwland et al. [38]	Retrospective	GCA	61	Extracranial GCA had a longer diagnostic delay. Other factors: generic symptoms, low incidence	Median 21 days (IQR 11–73.5) for cranial GCA; median 57 days (IQR 33–105) for extracranial GCA
Gorczyca et al. [39]	Retrospective	Kawasaki disease	27	Incomplete KD (lower incidence of lymphadenopathy, conjunctivitis) had a longer time to diagnosis	Complete KD: 7 days, incomplete KD: 11 days
Ugurlu et al. [40]	Retrospective	Behcet's syndrome	368	Longer in patients with only mucocutaneous symptoms (2.8 ± 2.2 years)	2.5 ± 2.1 years
Wang et al. [41]	Retrospective	Behcet's syndrome	170	Consecutive symptom onset separated by years, <1/5th of the patients had ≥2 presentations at onset, making the characteristic findings hard to ascertain	Mean 5.7 years
Sachetto et al. [42]	Retrospective	Behcet's syndrome	87	Mostly studied demographics	Mean 3 years

Table 1 (continued)

References	Type of study	Type of vasculitis	Number of patients	Causes of the diagnostic delay	Duration of delay
Pain et al. [43]	Prospective, in children and young people (≤ 6 years)	Behcet's syndrome	56	A rarity in this age group coupled with a low index of suspicion	Median 3.5 years (IQR 1.5–6.75)
Daoud et al. [44]	Retrospective	Behcet's syndrome	130	Late consultations, varied first clinical presentations	Average 53.5 ± 65.2 months
Ezeonyeji et al. [45]	Retrospective	GCA	65	Non-headache presentations like diplopia, jaw claudication	Average 36 days (range 2–140)
Tombetti and Sarzi-Puttini [72]	Review article	TAK	NA	Lack of clinical suspicion	NA

LVV large vessel vasculitis, *AAV* ANCA-associated vasculitis, *EGPA* eosinophilic granulomatosis with polyangiitis, *IQR* interquartile range, *GPA* granulomatosis with polyangiitis, *GCA* giant cell arteritis, *PMR* polymyalgia rheumatica, *TAK* Takayasu arteritis, *KD* Kawasaki disease, *CVA* cerebrovascular accident, *PUO* pyrexia of unknown origin, *NA* not available

of specific immunosuppression, which leads to damage accrual [56].

Awareness about the varied presentation of vasculitides is also poor among practitioners, as explored by a recent survey during the COVID-19 pandemic [16]. Less than half of the respondents could correctly identify the organs that could be potentially affected by ANCA-associated vasculitis, which is a cause for concern as the chances of missing organ-limited disease increase [16].

Disease-related factors

As a rule, the majority of primary systemic vasculitis cases have constitutional symptoms such as prolonged fever, malaise, arthralgia, and weight loss at onset, which may be the presenting feature in many cases and tends to portend a delay in arriving at a diagnosis [57]. These diseases are notorious for their heterogeneity [58]. Primary angiitis of the CNS and organ-limited or CNS-limited forms of GPA may have a headache as a predominant feature for a prolonged duration, with only prodromal symptoms, which may result in a significant diagnostic delay until a catastrophic event occurs [59].

AAV, in particular, is commonly misdiagnosed as an infection such as TB owing to clinical features such as hemoptysis coupled with granulomatous inflammation and nodules in the lung [51, 53]. The converse is rarely true when diseases like non-Hodgkin cutaneous T cell lymphoma, cutaneous leishmaniasis, or cocaine-induced midline destructive lesions have been misdiagnosed as GPA [51, 54, 60]. The spectrum and evolution of symptoms also influence the time to diagnosis. For instance, patients who present to an ENT specialist mostly present with organ-limited disease, as opposed to dramatic pulmonary or rapidly progressive glomerulonephritis that may present to the internist, making the diagnosis more apparent. In addition, the yield from an ENT biopsy is lower than that from a renal biopsy, contributing to the delay [26].

Behcet's syndrome is a variable vessel vasculitis in which longer delays are reported. We also observed that over the last decade, the duration of delay decreased in the cohorts of Behcet's syndrome, but the causes reported were mostly similar. In one of the early cohorts over 2 decades ago, the mean diagnostic delay was over 6 years, which was attributed to an overall low prevalence of the disease and the sheer heterogeneity in its presentation [61]. However, over the next decade, there has been a steady decline in the time to diagnosis, with improved awareness and diagnostics (Table 1). However, this decline has not been as evident in pediatric cohorts from the United Kingdom and Ireland [43]. Other evidence has been mostly anecdotal. Behcet's syndrome is classically described in the presence of oral and genital ulcers with a positive pathergy test. The disease presenting

in the absence of these symptoms tends to misguide the clinician in many cases, where the clinical suspicion is low. In addition, the positivity of the pathergy test ranges from 15 to 60% across cohorts [41, 62]. Therefore, unless the patients present to a rheumatologist or a physician experienced and sensitized toward other features of variable vessel vasculitis, the chances of missing this are quite high.

PAN is a disease for which most of the available evidence is anecdotal [63–65]. A recent international, multicentre "GLOBAL-PAN" study evaluated the clinical features and outcomes in systemic and cutaneous PAN, comparing and contrasting the two, but it was not designed to ascertain the causes for diagnostic delay nor was there any estimated duration of delay [66]. However, the authors opined that the heterogeneous presentation of the disease and common monogenic mimickers mostly contributed to delayed diagnosis in PAN [66]. Additional evidence is derived from isolated case reports or small case series with a presumably atypical presentation and refractory course. A series of three cases of neurological PAN illustrated that atypical presentations such as cerebral or spinal arterial aneurysms or non-specific presentations such as severe headaches may not prompt the physician to make a primary diagnosis of PAN, resulting in a delay in initiating treatment [65].

During the COVID-19 pandemic, many cases of systemic vasculitis were reported to be triggered following infection or vaccination [48]. There were also many cases of vasculitis, more AAV that were potentially missed or had a longer time to diagnose as they were labeled secondary vasculitis of COVID or vasculopathy before the definitive diagnosis was made.

Patient factors

LVV like GCA has a cranial and extracranial presentation. Evidence suggests that patients with an extracranial GCA at onset have a longer diagnostic delay, which may be due to both patient and physician factors, as non-rheumatologists may not be trained to exercise a high degree of suspicion for GCA in patients with non-specific symptoms such as fever, weight loss, malaise, arthralgia, diplopia, or jaw claudication, although the last two symptoms are relatively more suggestive [22, 38, 45]. In summary, patients who have a longer prodrome or a longer duration of constitutional symptoms tend to seek healthcare late, which may potentiate damage accrual by the time they present to the rheumatologist.

The other LVV, TAK, especially in childhood-onset disease, non-specific symptoms predominate, and across geographic areas, researchers have observed that pediatric TAK has a longer time to diagnosis than adolescent-to-adult-onset TAK, as these children present late. The absence of serological screening and diagnostic tests contributes to this, especially when the clinical examination is not robust [30–33].

Solutions to reduce the delay

One way to reduce diagnostic delay is to increase the number of trained, board-certified rheumatologists [3]. The workforce is grossly inadequate to cater to the growing need for specialist rheumatology care, which is projected to worsen over the next decade, although the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) are working to identify problem areas and develop models for workforce prediction to meet the growing requirements [67, 68]. Access to specialist care is also plagued by painful referral systems, where unless the general practitioner at the first point of contact recognizes the disease, vital diagnoses may be missed, leading to potentially catastrophic complications [21]. This condition worsens in developing countries [69]. In addition, equitable access to specialist care can hasten diagnosis and treatment initiation and prevent accrual of damage. There should be more education regarding the danger signs of vasculitis even in undergraduate medical education. This may be augmented by online teaching for postgraduates from rheumatology referral centers [70].

There must be improved awareness among emergency physicians to identify systemic vasculitis presenting with cutaneous manifestations, severe headache, or rapidly progressive renal failure such that they exercise a high index of suspicion to screen and refer or initiate emergent treatment that can save lives or organs or vision (like the dreaded anterior ischemic optic neuropathy of GCA, which can be suspected from a bedside fundus examination) [16, 71]. Routine screening of patients with interstitial lung disease for concomitant mononeuritis or the presence of ANCA antibodies will help in the early diagnosis of indolent MPO vasculitis. Clinicians must be aware of soft points suggesting systemic vasculitis such as constitutional symptoms (prolonged fever and weight loss), palpable purpura, mononeuritis multiplex, neutrophilic leukocytosis, and thrombocytosis. Urine microscopy can provide precious information about glomerular disease and is best evaluated by an expert conversant in recognizing various types of casts and abnormal cells. Some features may be deemed non-specific in isolation, but in the presence of supportive evidence of epistaxis, recurrent sinusitis, hemoptysis, and arthritis, one should exercise a strong degree of suspicion and investigate for AAV.

Conclusion

A relatively low incidence and the lack of exposure among general physicians, coupled with clinical heterogeneity of presentation portends a diagnostic delay in systemic vasculitis. Improving awareness among internists, and equitable and timely access to specialist rheumatological care can ensure

the initiation of emergent, definitive treatment leading to reduced damage accrual and a better quality of life with improved long-term outcomes.

The key takeaway is that it is essential to increase awareness among both the general public and healthcare practitioners regarding the early detection of vasculitis and the implementation of efficient referral systems with prompt access to investigative resources like ultrasound. Achieving this mandates the active participation and agreement of all stakeholders, including individual rheumatologists, various medical societies as well as policymakers.

Funding None.

Declarations

Conflict of interest The authors declare no potential conflicts of interest.

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Rheumatology International
https://doi.org/10.1007/s00296-023-05276-8

Rheumatology
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The impact of the COVID-19 pandemic on patients with systemic vasculitis: a single-centre retrospective study

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Received: 8 November 2022 / Accepted: 7 January 2023

Abstract

This study aimed to study the impact of the COVID-19 pandemic on patients living with systemic vasculitis in Kazakhstan. A single-centre retrospective study of the medical histories of 82 patients was carried out based on the regional clinical hospital of the city for all admissions with systemic vasculitis in the period from January 2019 to December 2021. The following qualitative (gender, disability, concomitant diseases) and quantitative (age, disease experience, laboratory data, etc.) variables were studied. To conduct the study, the criteria for the inclusion and exclusion of patients in the study were determined. According to the results of the study, there is a decrease in the number of hospitalized patients with vasculitis in the rheumatology department of the regional clinical hospital. Compared to 2019, in 2021, the number of hospitalized patients decreased by almost half (Table 1). Out of 82 cases, the most common was Takayasu disease (nonspecific aortoarteritis) (43.9%), IgA-vasculitis (Schenlein-Genoch disease) (31.71%), and they are typical mainly for females of rural origin, who were admitted to the hospital in a comorbid state ($p < 0.001$). 41.6% of patients have disabilities, and the majority of patients have a II disability group. The average body mass index is 24.2; 27 patients out of the total number of patients suffer from obesity. The most common clinical symptoms of patients with systemic vasculitis were injuries of the musculoskeletal system (75.6%). A negative average correlation was found between the indicators of the level of ESR and haemoglobin, the correlation coefficient is -0.535. The patients had concomitant diseases, such as diabetes mellitus, iron deficiency anaemia, coronary heart disease, hypertension, gastrointestinal tract diseases and hepatitis. Women of reproductive age from rural areas are often diagnosed with systemic vasculitis. A high rate of disability revealed among the patients can be explained by two main factors, the first is that the patients consulted the doctors untimely and the second is that the medical community are insufficiently informed about the management of autoimmune rheumatic diseases, in particular about systemic vasculitis, which hinders timely diagnosis and treatment, respectively. Patients, included in this survey, were mostly suffering from diseases of the musculoskeletal system, but depending on the type of vasculitis, other organs and systems may be affected.

Keywords Vasculitis · ANCA-associated vasculitis · Systemic vasculitis · COVID-19

Introduction

Vasculitis is a group of diseases that can lead to various complex disorders of different organs and systems [1]. Systemic vasculitis has complicated, so it is problematic to identify its main causes. A lot of cases are classified as idiopathic vasculitis as the disease could occur due to unknown reasons. Arterial blood vessels could also suffer from vasculitis as well as venous blood vessels, thus affecting not only separate organs but a system or even several systems as well.

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Published online: 16 January 2023

Table 1 Frequency of patients with systemic vasculitis over 3 years

Year	Frequency	%	*p*-value
2019	42	51.2	$\chi^2 = 12.463^a$; $p = 0.002$
2020	23	28.0	
2021	17	20.7	
Total	82	100.0	

We could say that in the case of vasculitis, it is necessary to study several different pathophysiological mechanisms and a wide clinical spectrum.

But before studying this illness, it is better to consider some classification issues. A lot of authors are talking about the calibre of blood vessels, classifying them as small, medium or large vessels. However, this classification does not consider the diversity of neighbours of the same calibre, and their specific role in several anatomical areas in response to irritants, stress and recovery, which, in its turn, determine the characteristics of diseases [2, 3]. Vasculitis can be classified based on various indicators, such as the size of the affected vessels, causes, pathogenesis, and their types, as well as clinical signs [4].

The prevalence of systemic vasculitis varies widely depending on geographical areas and different population groups [5]. These changes can be caused by various factors, for example, genetic factors, which manifest themselves in the form of gene polymorphism and changes in the environment (various infections, chemical exposure, ultraviolet radiation, as well as factors related to the seasons) [6–8].

The research on systemic vasculitis was carried out using data banks of individual centres in some regions. However, it is not enough to determine the epidemiology of such a widespread group of diseases as vasculitis. High-quality epidemiological studies require a long period, or they could be conducted after analyzing much more cases, but such approach will negatively affect the quality of research [9].

The pathogenesis of systemic vasculitis is still completely unclear, even though a lot of research is being conducted in this area. At the present stage, there are no uniform tests and specific diagnostic criteria for many types of systemic vasculitis, so vasculitis is diagnosed only by the exclusion approach when other cases are excluded. Nevertheless, fast and reliable diagnosis is incredibly important in these conditions, as it allows to start of timely treatment and avoids the progression of insufficiency of various organs and systems with irreversible damage, which often leads to disability [1].

Advances in the field of medical treatment of vasculitis have led to the fact that patients began to live longer, and they have also influenced positively the prognosis of patients' lives [10]. Although in this field, healthcare system has achieved success in the treatment of that nosology, its treatment remains a difficult task, taking into account the delicate balance between the risks of relapse of the disease and the negative consequences of immunosuppressive therapy, primarily serious infections. As a result, the expansion of the use of targeted therapy aimed at reducing dependence on corticosteroids and other nonspecific immunosuppressants has come to the fore [11].

Regretfully, relapses of the disorder occur quite often and chronic circulatory complications are a source of considerable morbidity [12].

Since the beginning of the COVID-19 pandemic, vasculitis-like symptoms and full-blown vasculitis syndromes have been mainly documented in children and adolescents cases [13]. The risk of COVID-19 infection and related complications increases for patients with pre-existing diseases. Patients with chronic rheumatological diseases and vasculitis are at high risk of infection due to underlying immune disorders and the effects of glucocorticosteroids, as well as other immunosuppressive drugs [14]. COVID-19 is a syndrome of SARS-CoV-2, which has the character of a multiorgan lesion and also leads to a violation of the circulatory system. Inflammation of endothelial cells occurs in blood vessels and contributes to some disorders, such as tissue hypoperfusion, damage, thrombosis and vascular disorders at different stages of the disease (acute, subacute and possibly chronic) [15].

Some features of the visualization of lung lesions of such patients may imitate COVID-19. CT images of major background diseases may obscure or erase the signs of COVID-19, especially in the early stages of infection. Therefore, it will be difficult to differentiate superimposed SARS-CoV-2 infection from the main autoimmune lung disease, and interpretation should be based on serological data and clinical conditions.

Nowadays, it is vital to use the patient-oriented treatment approach since it is important to involve patients in joint decision-making to assess short- and long-term risks of the disease, as well as treatment methods. This would help to increase the overall efficiency of medical professionals' work [11].

Materials and methods

A single-centre retrospective study of the medical histories of 82 patients was carried out based on the data from the city regional clinical hospital. Taking all admissions with systemic vasculitis in the period from January 2019 to December 2021, there were 18 males (22%) and 64 females (78%), $p < 0{,}001$. The following qualitative (gender, disability, concomitant diseases) and quantitative (age, disease experience, laboratory data, etc.) variables were considered during the research.

Table 2 Types of vasculitis in patients hospitalized in the hospital

Types of vasculitis	%
Patients with granulomatosis with polyangiitis (Wegener's granulomatosis)	3.66
Patients with Takayasu disease (nonspecific aortoarteritis)	43.90
Patients with IgA-vasculitis (Schenlein-Henoch disease, hemorrhagic vasculitis)	31.71
Patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)	1.22
Patients with Still's disease (systemic necrotizing vasculitis)	7.32
Patients with Behcet's disease	3.66
Patients with nodular polyarteritis	6.10
Patients with systemic variable vasculitis (Kogan's syndrome)	2.44
Total	100

The following criteria were determined to include or exclude the patients in the study:

Inclusion criteria: patients with systemic vasculitis over the age of 18.

Exclusion criteria: patients under the age of 18, with pregnancy, cancer, patients with neurological diseases, mental disorders, intoxication with psychotropic drugs and alcoholism.

The patients were divided into 2 groups, where the first group was on steroid therapy (41 patients) at the time of hospitalization, and the second group of patients did not take steroid drugs (41 patients).

Statistical data processing was carried out using the IBM SPSS Statistics statistical package, version 20. To describe quantitative data, we used the mean (M) ± standard deviation (SD) if the normal distribution was subjected, as well as median (Me) and interquartile range (IQR) were used if the normal distribution was not subjected; nominal qualitative data were described by absolute and relative frequencies (%). The reliability of the differences in values of nominal qualitative data was performed using the Pearson X^2 test. The Student t test was used when the data had two independent groups with normal distributions. An analogue of the Student's t test is the Mann–Whitney U Test (Me; IQR). Pearson correlation was used to find the strength and direction of the relationship between two quantitative variables. Regression analysis was carried out to determine linear relationships between two variables.

Results

According to the results of the study, there is a decrease in the number of in-door patients with vasculitis in the rheumatology department of the regional clinical hospital: 2019–42 patients (51.2%), 2020–23 (28%), 2021–17 (20.7%) $p = 0.002$ (Table 1).

Taking 82 cases, Takayasu disease (nonspecific aortoarteritis) is common with patients—36 cases (43.9%), IgA-vasculitis (Schenlein-Genoch disease)–26 cases (31.71%), mainly for females of rural origin who were admitted to hospital in a comorbid state ($p < 0.001$) (Table 2).

Table 3 Time from the onset of the disease to the diagnosis

Types of vasculitis	Mean, months
Takayasu disease, $n = 36$	M = 16.31 (95% CI: 5.15–27.46)
IgA-vasculitis, $n = 26$	M = 8.96(95% CI:− 4.02–21.94)
Still's disease, $n = 6$	M = 5.17 (95% CI:− 0.032–10.66)

Table 4 Portrait of a patient with vasculitis

Variables	Frequency	%
Place of living ($\chi^2 = 9.561^a$; $p = 0.002$)		
Rural	55	67.1
Urban	27	32.9
Gender identity ($\chi^2 = 25.805^a$; $p < 0.001$)		
Male	18	22.0
Female	64	78.0
Disability		
Disabled people of group I	3	3.66
Disabled people of group II	21	25.61
Disabled people of group III	10	12.20
Without disability	48	58.54
Ability to move independently		
Yes	82	100.0
Total	82	100.00

The time from the onset of the disease to the diagnosis of Takayasu's disease (non-specific aorthoarteritis) n = 36 is M = 16.31 (95% CI: 5.15–27.46); IgA-vasculitis (Schenlein-Genoch disease) n = 26—M = 8.96 (95% CI:− 4.02–21.94); Still's disease (systematic necrotic vasculitis) $n = 6$—M = 5.17 (95%CI:− 0.032–10.66) (Table 3).

Portrait of patients with vasculitis treated in the rheumatology department of the regional clinical hospital: gender—18 male (22%), 64 female (78%) ($p < 0.001$); place of residence—rural area 55 (67.1%), city 27 (32.9%) ($p < 0.001$); disability–3 people disabled people, the first

Table 5 Patient data by stages of obesity

Variables	Frequency	%	*p*-value
Patients with pre-obesity			
No	63	76.8	$\chi^2 = 78.049^a$; $p < 0.001$
Yes	19	23.2	
Patients with class I obesity			
No	75	91.5	$\chi^2 = 56.390^a$; $p < 0.001$
Yes	7	8.5	
Patients with class II obesity			
No	81	98.8	$\chi^2 = 78.049^a$; $p < 0.001$
Yes	1	1.2	
Patients with class III obesity			
No	82	100.0	
Total	82	100.0	

group (3.66%), 21 patients with the second disability group (25.61%), 10 patients with the third group (12.2%), 48 patients have no disability (58.4%) and all 82 patients can move independently (Table 4); obesity—the average body mass index is 24.2 (24;6), min = 17, max (37), 19 patients with pre-obesity, 7 patients with the I class and 1 patient with the II class of obesity (Table 5). Their main clinical symptoms were: musculoskeletal system damage (75.6%), gastrointestinal tract damage (57.3%), skin damage (48.8%), peripheral vascular damage (37.8%), cardiovascular system damage (31.7%), arthralgia (50.6%), myalgia (48.2%), lung damage (9.8%), nervous system damage (8.5%), ENT organ damage (7.3%), visual organ damage (4.9%) and endocrine system damage (2.4%) (Table 6).

At the time of admission, 45 patients had elevated ESR (54,9%) $p = 0.377$, with leukocytosis—15 (18,3%) $p < 0,001$, with CRP more than 5 mg/l–38 (46.3%) $p = 0.508$, patients with positive ANA (6 cases), ANCA (5), ASO (7), rheumatoid factor (1), anti-CCP (1), anti-ds DNA (11) and the presence of LE cells (2) $p < 0,001$.

The average age of patients at the onset of the disease was 30 years, while the average age of patients at the time of examination was 36 years. Therefore, the majority of patients were of reproductive age.

41 patients were on steroid therapy. In the 1 group, the average ESR level was 18.17 (15;20), in the 2 – 23.07 (20;26); the average level of CRP (C-reactive protein) group 1 - 16.07 (5;18), group 2 - 17.76 (7;15); the average haemoglobin level group 1 - 119.54 (121;31), group 2 - 116.90 (23.624) (Table 7).

A negative average correlation was found between the indicators of the level of ESR and haemoglobin, the correlation coefficient is − 0.535 (Table 8).

Concomitant diseases have been reported, including diabetes mellitus, iron deficiency anaemia, coronary heart

Table 6 Damage to organs and systems

Variables	Frequency	%	*p*-value
Organs of vision			
No	78	95.1	$\chi^2 = 66.780$; $p < 0.001$
Yes	4	4.9	
Nervous system			
No	75	91.5	$\chi^2 = 56.390^a$; $p < 0.001$
Yes	7	8.5	
Genitourinary system			
No	63	76.8	$\chi^2 = 23.610^a$; $p < 0.001$
Yes	19	23.2	
Lungs			
No	74	90.2	$\chi^2 = 53.122^a$; $p < 0.001$
Yes	8	9.8	
Cardiovascular system			
No	56	68.3	$\chi^2 = 10.976^a$; $p = 0.001$
Yes	26	31.7	
Peripheral vessels			
No	51	62.2	$\chi^2 = 4.878^a$; $p = 0.027$
Yes	31	37.8	
Gastrointestinal tract			
No	35	42.7	$\chi^2 = 1.756^a$; $p = 0.185$
Yes	47	57.3	
Musculoskeletal system			
No	20	24.4	$\chi^2 = 21.512^a$; $p < 0,001$
Yes	62	75.6	
Skin and its appendages			
No	42	51.2	$\chi^2 = .049^a$; $p = 0.825$
Yes	40	48.8	
Endocrine system			
No	80	97.6	$\chi^2 = 74.195^a$; $p < 0.001$
Yes	2	2.4	
ENT organs			
No	76	92.7	$\chi^2 = 59.756^a$; $p < 0.001$
Yes	6	7.3	
Total	82	100.0	

Table 7 Results of laboratory data of patients undergoing steroid therapy

Indicator	Mean (Me; IQR)	Min	Max
ESR level indicator: (mm/hr), $p = 0.142$			
No (steroid therapy)	23.07 (20;26)	2	65
Yes (steroid therapy)	18.17 (15;20)	2	54
Indicator of the level of CRP (C-reactive protein) mg/ l, $p = 0.148$			
No (steroid therapy)	17.76 (7;15)	0	241
Yes (steroid therapy)	16.07 (5;18)	0	239
Haemoglobin level index, $p = 0.633$			
No (steroid therapy)	116.90 (23.624)	67	160
Yes (steroid therapy)	119.54 (121;31)	72	157
Mann–Whitney U test			

Table 8 Correlation between X and Y quantitative variables (Pearson)

Correlation between X and Y quantitative variables	Correlation; significance
Correlation between level of CRP and ESR	r = 0.123; $p = 0.270$
Correlation between CRP and hemoglobin levels	r = − 0.172; $p = 0.123$
Correlation between ESR and hemoglobin levels	r = − 0.535; $p < 0.001$

disease, hypertension, gastrointestinal tract diseases, hepatitis, etc.

Discussion

Takayasu disease is an uncommon inflammatory state that affects the largest blood vessels and involves mostly young patients under the age of 40. The overall epidemiology of the disease is still unidentified [16]. Non-specific systemic symptoms, which are conjugated by no pulse and different types of ischaemic symptoms, should be considered along with deep diagnostic imaging. Timely correct diagnosis and necessary therapy can prevent the patient from risky complications [17].

Takayasu disease was first described in Japan. Although this disease is widespread throughout the world, it was believed by scientists that this disease is more common for people of Asian origin since their cases are mostly reported by those countries. However, this report has not yet been confirmed by high-quality epidemiological studies [16].

Based on data from the 1980s in Japan, the incidence rate in Japan is equal to the incidence rate of the European population, that is, 1–2 per million people per year [18]. Besides, a study, conducted in Norway among representatives of different ethnic backgrounds, revealed a predominance of small groups of people of African (108 per million) and Asian (71 per million) [19].

The best option for determining the origin is to determine the place of birth of all four grandparents of a person, however, this determination is usually impossible, which, in its turn, leads to dependence on the self-assessment of the genealogy. The above-mentioned factors have significantly affected the accuracy of epidemiological studies of systemic vasculitis and must be taken into account when evaluating epidemiological data on these diseases [1].

According to the study, the most common type of systemic vasculitis diagnosed in patients is Takayasu arteritis (43.9%).

The treatment of many autoimmune diseases, in particular systemic vasculitis, is a polysyllabic process. Informing patients about the starting manifestations of this disease and tracking possible side effects plays an important role, since specialists, who follow such an approach, improve the prognosis of the disease thus minimizing the risks of disability and mortality. In the case of systemic vasculitis, multiple organ damage needs a multidisciplinary approach to the course of patients' treatment [10]. The prognosis of Takayasu disease is most likely getting better with lower lethality rates registered in the last few years, perhaps due to the use of more effective medical therapy in addition to the use of endovascular interventions when required and accessible [20].

There was a high percentage of disability among the patients. Advances in the field of drug treatment of systemic vasculitis have led to much longer life of patients. Nevertheless, a significant proportion of patients with vasculitis continue to be disabled or less productive, secondary to their diagnosis, while indicators of disability and loss of income have barely changed over the past 35 years. Identifying the factors associated with illness and work, which are considered the riskiest as they could lead to work restriction, can help in the development of policies and programs to optimize beneficial working conditions and improve support for patients with vasculitis [10].

Systemic vasculitis is a multisystem disease, which often affects vital organs. And this study proved that vasculitis is a multisystem disease. Depending on the type of vasculitis, various organs and systems were involved in the process. Most often, one of the first manifestations of the disease was a lesion of the musculoskeletal system. There was also a lesion of the gastrointestinal tract, which has a possible connection with the use of long-term Glucocorticosteroids therapy. Depending on the specific type of vasculitis, there were other manifestations of the disease.

The use of immunosuppressive drugs remains the basis for the treatment of systemic vasculitis, although, as in rheumatology in general, the role of genetically engineered biological drugs is increasing in the treatment of systemic vasculitis. More scientific research is necessary to better understand the disease's pathomechanisms and implement new medications and therapy regimens so that disease periods of remission are more prolonged, and treatments more successful, resulting in better life quality for patients [17].

The treatment of autoimmune diseases, in particular systemic vasculitis, is a complex process. By informing patients about the early signs and symptoms of this disease, as well as monitoring possible side effects, specialists increase the likelihood of a favourable outcome, minimizing the risks of disability and mortality. It is quite significant to consider the fact that it is extremely important to start immediate

treatment of patients with aggressive diseases. Damage of several organs in the case of systemic vasculitis requires a multidisciplinary approach to the treatment of patients.

According to the results of the study, there is a decrease in the number of admitted patients with vasculitis in the rheumatology department of the regional clinical hospital: 2019–42 patients (51.2%), 2020–23 (28%), 2021–17 (20.7%) $p = 0.002$. A possible reason for the decrease in the number of patients is the COVID-19 pandemic, which could also affect the quality of life of patients. A survey of a research network focused on patients with vasculitis revealed a high level of concern about COVID-19 in patients with vasculitis. The use of immunosuppression, old age, female gender and concomitant lung diseases affected the level of anxiety. These concerns had a direct impact on avoiding visiting a doctor and conducting laboratory and other tests. An alarming number of patients (10.5%) stopped immunosuppression without consulting their doctor. In addition, temporary discontinuation of rituximab (7.5%) or refusal (13.3%) of further rituximab administration was reported [24].

The incidence of metabolic syndrome (MetS) tends to be increased among patients with rheumatic diseases, and it ranges from 14 to 62.8%. [21] Metabolic syndrome is described by a compound of several cardiovascular risk factors (age, sex, smoking, arterial hypertension, and dyslipidemia) that assume additional cardiovascular morbidity that is more important than the sum of the risk factors related to each component [22]. Scientific studies have presented that atherosclerosis is accelerated in patients with rheumatic diseases, particularly in systemic vasculitis, while the causal reasons have not yet been completely clarified [23].

According to our study, of 82 patients, 27 patients were found to be obese in different forms (pre-obesity, obesity of 1 and 2 classes). There was observed a gain of weight, probably as a side effect of medications such as Glucocorticosteroids. Some studies have shown that patients with ANCA-associated vasculitis often gain weight, especially during the first year after diagnosis. In the cohort of patients included in the study on Wegener's granulomatosis Etanercept (WGET), the authors showed that 22.3% of the total number of patients with granulomatosis with polyangiitis gained at least 10 kg during the first year after diagnosis [25].

Early access of patients to the doctor and awareness of doctors are key factors in verifying the diagnosis. As shown by the results of an international survey that was developed to study the knowledge and perceptions of medical professionals about the diagnosis and treatment of ANCA-associated vasculitis, the perception of systemic vasculitis differs in different countries. This study also revealed the need to update knowledge and awareness of small vessel vasculitis among the entire medical community since its inception [26]. To increase the level of knowledge about systemic vasculitis, which doctors of outpatient services and hospitals of various profiles may encounter in practice, it is necessary to develop educational programs and resources for continuing professional education for doctors with an emphasis on rare autoimmune pathologies, and in particular systemic vasculitis.

Limitations

The study has limitations as it was a retrospective study of a small cohort in one centre, and therefore, our results cannot be generalized without further investigation. However, conducting prospective studies of this rare disease is a difficult task.

Conclusion

Thus, it can be concluded that systemic vasculitis is most often found in women of reproductive age living in rural areas. A high level of disability was observed among patients, and this could be explained by two main factors, the first is the late treatment of patients, and the second is that the medical community is insufficiently informed about the management of systemic vasculitis, which prevents timely diagnosis and treatment, respectively. Although, as a result of our study, the immunological parameters of patients with vasculitis during the pandemic did not differ from the pre-pandemic period, the COVID-19 pandemic had a significant indirect effect on patients with systemic vasculitis. According to our study, patients' access to medical care has almost halved compared to the pre-pandemic period.

The high frequency of systemic vasculitis among rural patients may be due to the significant remoteness of large areas from specialized medical institutions. To eliminate this problem, a comprehensive approach is needed, which includes increasing the level of education of rural residents and raising awareness of primary health care doctors in rural areas about autoimmune rheumatic diseases, in particular systemic vasculitis, telemedicine, etc. The most common case in this study was diseases of the musculoskeletal system, but depending on the type of vasculitis, other organs and systems may be affected, in this regard, the diagnosis and treatment of systemic vasculitis should be interdisciplinary.

High awareness of doctors about autoimmune diseases, early and immediate diagnosis, referral to a rheumatologist and timely treatment are the key to good outcomes in patients and a successful prognosis. Many clinical questions need to be solved in the future, but to answer them, prospective multicenter studies are needed.

Timely detection and proper treatment of vasculitis (newly diagnosed or recurrent disease) remain a priority,

and the question of whether or not to change the treatment protocols for systemic vasculitis during COVID-19 remains open.

Author contribution All co-authors contributed substantially to the concept, formulation, searches of relevant articles, and revisions. They approve the final version of the manuscript and take full responsibility for all aspects of the work.

Data availability The data that support the finding of this study are available on a reasonable request from the corresponding author.

Declarations

Conflict of interest The authors have stated that there are no conflicts of interest in connection with this article.

Ethical approval This study was approved by the Local Ethics Committee at South Kazakhstan Medical Academy, protocol N1, 2020.

Informed consent The requirement for additional written informed consent was waived because of the retrospective design of this study and the use of anonymous patient data.

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Rheumatology International
https://doi.org/10.1007/s00296-024-05533-4

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Clinical and anamnestic features of patients with systemic vasculitis: a single-center retrospective study

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Received: 30 October 2023 / Accepted: 2 January 2024

Abstract

Systemic vasculitides are the most complex and problematic autoimmune rheumatic diseases characterized by affections of large, medium, or small vessels. Although the immunopathogenesis of vasculitides is thoroughly studied, the epidemiology and etiology are poorly explored. The main triggers of vasculitides are environmental, genetic, and various infectious factors. Diagnosis of vasculitides is complicated due to the non-specific nature of their symptoms. Vasculitides affect various organ systems with abrupt or slow (weeks–months) development of symptoms. This study aims to analyze the demographic and clinical-anamnestic characteristics of patients with systemic vasculitides in a single centre before and during the COVID-19 pandemic in Kazakhstan. A single-centre retrospective study of medical records of 80 patients above 18 years was conducted in the Almaty City Rheumatology Center. Medical records of 24 males (30%) and 56 females (70%) with systemic vasculitides, diagnosed from January 2019 to December 2021, were analyzed. Age, gender, damaged organ systems, disability, concomitant diseases, disease experience, laboratory data, and other variables were recorded. The records of hospitalized patients with systemic vasculitides were analyzed. Of 80 patients registered in 2019–2021, the most common were those with IgA vasculitis ($n=32$, 40%), Takayasu arteritis ($n=17$, 21.25%), and granulomatosis with polyangiitis ($n=12$, 15%). Behçet disease was diagnosed less frequently ($n=9$, 11.25%). Patients with systemic vasculitides had pre-obesity ($n=19$), class 1 obesity ($n=13$), and class 2 obesity ($n=2$). Musculoskeletal affections were present in 52 patients (65%). Gastrointestinal, cutaneous, and cardiovascular affections were recorded in 45 (56.3%), 37 (46.3%), and 39 (48.8%) cases, respectively. Only 8 patients (10%) had affections of the nervous system. Most patients had elevated C-reactive protein ($n=29$, 36.3%) and leukocytosis ($n=33$, 41.3%). One-third of patients with vasculitides had a history of abortions. Musculoskeletal, cutaneous, gastrointestinal, and cardiovascular affections are common in patients with systemic vasculitides. Obesity is a frequent comorbidity in vasculitides. Comorbidities and abortions complicate the disease course and its management.

Keywords Systemic vasculitis · IgA-vasculitis · Takayasu disease · Systemic vasculitides · Disability

Introduction

Systemic vasculitides are rare inflammatory diseases that affect vessels of various calibers, leading to complex organ system disorders [1, 2]. Vascular inflammation in these patients can lead to the reduction of blood flow and ischemic damage [3]. Vasculitides affect subjects of all ages and manifest variably, from mild and transient to life-threatening conditions [4, 5].

The names and definitions of systemic vasculitides have been revised due to improved knowledge and perceptions which are reflected in the 2012 International Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitides. The exact prevalence of vasculitides is difficult to estimate due to rarity and diagnostic uncertainties, though new categories and revisions of names and definitions in the 2012 Chapel Hill Nomenclature can help resolve related issues [4]. Systemic vasculitides remain the most complex and problematic autoimmune diseases, categorized into vasculitides of large, medium, and small vessels [6].

Diagnosis of vasculitides is confounded by numerous non-specific factors and similarities with other rheumatic

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Published online: 06 February 2024

diseases. The disease variably affects different organ systems with abrupt or insidious manifestations over weeks to months, causing diagnostic delays. These delays negatively affect the patient's health and quality of life. Minimizing diagnostic delays is therefore crucial for improving prognosis [7].

Vascular imaging advances have improved diagnostic workups and therapies for vasculitides. Such advances are mainly due to non-invasive visualization techniques [8]. The improved diagnosis of vasculitides has allowed estimating their prevalence worldwide [9].

Although the pathophysiology of vasculitides is explored in numerous studies, the exact etiological factors are still unknown. The main triggers are environmental, genetic, and various infectious agents [9].

This study aims to assess the demographic and clinical-anamnestic characteristics of patients with systemic vasculitis in Kazakhstan in a single centre before and during the pandemic.

Materials and methods

Medical notes of 80 patients over 18 years, who were hospitalized at the Almaty City Rheumatology Center in January 2019–December 2021, were analyzed. There were 24 males (30%) and 56 females (70%). The records included information about patients' age, gender, timelines of diagnosis, specifics of involved organ systems, presence of disabilities, and comorbidities, and laboratory data.

Statistical analyses

Statistical analysis was conducted with IBM SPSS Statistics, version 26. Normally distributed data were reported as mean (M) ± standard deviation (SD), whereas abnormally distributed data as median (Me) and interquartile range (IQR). Nominal data were reported in absolute values and frequencies (%).

Ethics approval

The Local Ethics Committee at South Kazakhstan Medical Academy approved this study (protocol N1, 2020). The requirement for written informed consent was waived due to retrospective design and anonymized data processing. To collect and process medical notes of patients, the state municipal enterprise "City Rheumatology Center" of Almaty City Healthcare provided permission to process data from the hospital archive (01.1-04 N398; August 17, 2022).

Table 1 Frequency of patients with systemic vasculitis

Year	*N*	%
2019	32	40
2020	39	48.8
2021	9	11.2
Total	80	100

Results

The results of systemic vasculitis patients who were hospitalized at the Rheumatology Center of Almaty in 2019, 2020, and 2021 were analyzed. The three-year distribution of patients is presented in frequencies in Table 1. The most common cases were IgA vasculitis ($n=32$, 40%), Takayasu arteritis ($n=17$, 21.25%), and granulomatosis with polyangiitis ($n=12$, 15%). Behçet disease was recorded less frequently ($n=9$, 11.25%) (Table 2).

The available records of timelines from disease onset to definite diagnosis are presented in Table 3. Notably, Behçet disease diagnosis turned the most problematic and time-consuming.

Sociodemographic data are presented in Table 4. Importantly, there were more females than males (70% vs. 30%, respectively). The majority of patients ($n=50$, 62.5%) had comorbidities such as type 2 diabetes mellitus and arterial hypertension.

Table 2 Types of systemic vasculitides recorded in the Rheumatology Center of Almaty

Recorded vasculitides	*N*	%
Granulomatosis with polyangiitis	12	15
Takayasu arteritis	17	21.25
IgA-vasculitis	32	40
Behçet disease	9	11.25
Polyarteritis nodosa	1	1.25
Microscopic polyangiitis	4	5
Giant-cell arteritis	2	2.5
Cryoglobulinemic vasculitis	1	1.25
Cutaneous vasculitis	1	1.25
Hepatitis C virus-related vasculitis	1	1.25
Total	80	100

Table 3 Timelines from vasculitis onset to definite diagnosis

Types of vasculitis	Mean duration in months (95% CIs)
Takayasu disease ($n=17$)	4.9 (95% CI 1.2–8.57)
IgA vasculitis ($n=32$)	5.53 (95% CI 0.21–10.84)
Granulomatosis with polyangiitis ($n=12$)	4.16 (95% CI 0.27–8.05)
Behçet disease ($n=9$)	10.5 (95% CI 2.92–18.08)

Table 4 Sociodemographic and clinical description of patients with systemic vasculitides

Variables	*N*	%
Place of residence		
Rural	16	20
Urban	64	80
Gender		
Male	24	30
Female	56	70
Disability		
Group I disabled patients	1	1.3
Group II disabled patients	3	3.8
Group III disabled patients	6	7.5
Patients without disabilities	70	87.5
Employment status		
Employed patients	19	23.8
Unemployed patients	47	58.8
Ability to move independently		
Yes	79	98.8
No	1	1.3
Complications of the main diagnosis		
Present	34	42.5
Absent	46	57.5
Comorbidities		
Present	50	62.5
Absent	30	37.5

In patients with systemic vasculitides, various degrees of obesity were recorded (Table 5): 19 patients were at the pre-obesity stage, 13 patients suffered from class 1 obesity, and two patients had class 2 obesity.

Organ system involvements are presented in Table 6. Musculoskeletal involvement was most commonly reported ($n = 52$, 65%). Cutaneous and gastrointestinal lesions were frequently diagnosed in patients with IgA vasculitis. Peripheral vascular lesions were frequent in patients with Takayasu arteritis.

Table 5 Obesity in patients with systemic vasculitides

Variables	*N*	%
Patients with pre-obesity		
No	61	76.3
Yes	19	23.8
Patients with class 1 obesity		
No	67	83.8
Yes	13	16.3
Patients with class 2 obesity		
No	78	97.5
Yes	2	2.5
Patients with class 3 obesity		
No	80	100
Yes	–	–

Table 6 Organ system involvement in patients with systemic vasculitides

Variables	*N*	%
Eye		
Yes	12	15
No	68	85
Nervous system		
Yes	8	10
No	72	90
Genitourinary system		
Yes	31	38.8
No	49	61.3
Lungs		
Yes	14	17.5
No	66	82.5
Cardiovascular system		
Yes	39	48.8
No	41	51.2
Peripheral vessels		
Yes	26	32.5
No	54	67.5
Gastrointestinal tract		
Yes	45	56.3
No	35	43.8
Musculoskeletal system		
Yes	52	65
No	28	35
Skin and its appendages		
Yes	37	46.3
No	43	53.8
Endocrine system		
Yes	12	15
No	68	85
Total	80	100

Most patients had elevated levels of C-reactive protein ($n = 29$, 36%) and white blood cells ($n = 33$, 41%) (Table 7). Nine patients (11%) had positive pANCA.

Past medical history is presented in Table 8. Anemia ($n = 26$, 32.5%), abortions ($n = 23$, 29%), and hepatitis B ($n = 15$, 19%) were most frequently recorded.

Finally, current drug therapies are presented in Table 9. Most patients were on corticosteroid therapies ($n = 72$, 90%) and less than one-third were on biologic therapies ($n = 21$, 26%).

Table 7 Laboratory data of patients with systemic vasculitides

Variables	*N*	%
Patients with positive rheumatoid factor		
Yes	25	32.5
No	55	67.5
Patients with positive Anti-CCP		
Yes	5	6.3
No	75	93.8
Patients with elevated antistreptolysin-O		
Yes	27	31.8
No	58	68.2
Patients with elevated CRP (more than 5 mg/l)		
Yes	29	36.3
No	51	63.7
Patients with positive Anti-ds DNA		
Yes	13	16.3
No	67	83.7
Patients with positive ANA		
Yes	8	10.0
No	72	90.0
Patients with positive p-ANCA		
Yes	9	11.3
No	71	88.8
Patients with elevated white blood cells		
Yes	33	41.3
No	47	58.8
Total	80	100

Table 8 Diseases recorded as past medical history of patients with systemic vasculitides

Variables	*N*	%
Tuberculosis		
Yes	2	2.5
No	78	97.5
Myocardial infarction or stroke		
Yes	8	10
No	72	90
Hepatitis B		
Yes	15	18.8
No	65	81.3
Anemia		
Yes	26	32.5
No	54	67.5
Abortion (in females)		
Yes	23	28.7
No	57	71.2

Table 9 Current drug therapies of patients with systemic vasculitides

Variables	*N*	%
Corticosteroid therapy		
Yes	72	90
No	8	10
Biologic therapy		
Yes	21	26.2
No	59	73.8
Cytostatic drug therapy		
Yes	23	28.7
No	57	71.3

Discussion

Based on the results of this single-centre study in Almaty, IgA vasculitis and Takayasu arteritis were frequently diagnosed in 2019–2021. Such results are consistent with our previous analyses in a regional centre of rheumatology [10].

Importantly, IgA vasculitis is less common in adults compared to children [9]. Overall, childhood vasculitis has an annual incidence of 6.2–24/100,000 whereas adult vasculitis is estimated at the level of 0.8–1.8/100,000. Caucasian and Asian subjects suffer more frequently from IgA vasculitis than Black subjects [11]. Our results suggest that IgA vasculitis was the most frequent type of vasculitis in subjects above 18 years. Based on literature data, environmental factors may confound the distribution of IgA vasculitis [12].

Reportedly, Takayasu arteritis frequently affects young Asian women [13]. In our study, 17 subjects were diagnosed with Takayasu arteritis and 16 of them were females. Our study revealed that 47 (58.8%) of patients with systemic vasculitides were unemployed. Patients with rheumatic diseases often suffer from work disability, necessitating to create flexible working conditions for this group of subjects [14].

Work disability due to health issues leads to productivity losses. These losses occur in both paid and unpaid work activities. Understanding the causes and predictors of productivity losses can help develop flexible working conditions [15]. Paradoxically, no vasculitis characteristics, such as disease activity, subtype, therapies, or ANCA status, have been associated with work disability [16].

Comorbidities are common in rheumatic musculoskeletal diseases and should be comprehensively addressed during diagnostic work-up [17]. Comorbidities in systemic vasculitides negatively affect the quality of life, morbidity, and mortality [18].

Hepatitis B positivity was detected in 14% of our patients with systemic vasculitides. Hepatitis B virus may act as a triggering and predictive factor in vasculitis. Accumulating evidence suggests an association of viral pathogens with the development of vasculitis with cutaneous and other organ

system involvements [19, 20]. Direct viral invasion in the vascular endothelium, vascular wall damage, and autoimmune responses stimulate autoreactive B cells and negatively affect regulatory T cells' function [21, 22].

Viruses, including SARS-CoV-2, are associated with a variety of vasculitides [23]. Latent viral infections may reactivate due to immunosuppressive therapies [24]. Certain vaccinations, including COVID-19 vaccinations, have been associated with the onset of vasculitides [25]. Further research is warranted to better understand the role of viruses and vaccines in developing systemic vasculitides.

Various primary vasculitides, including Takayasu arteritis, polyarteritis nodosa, ANCA-associated vasculitis, IgA vasculitis, and Behçet disease affect young women in their reproductive years [26]. In our study, 23 (28.7%) women reported abortions in their past medical history.

Immunosuppressive therapies may affect maternal, fetal, and pregnancy outcomes. With advances in new immunosuppressive therapies, these outcomes may improve for pregnant women with ANCA-associated vasculitis [24, 27–29].

Spontaneous abortion is one of the most common obstetric complications in Takayasu arteritis [30]. Achieving stable remission in vasculitis is a precondition for safer conception and pregnancy [31]. Pregnant women with vasculitis should be consulted by a multidisciplinary team of specialists to prevent exacerbations and adverse drug reactions [32, 33].

Excessive fat accumulation increases health risks, including the development of inflammatory and autoimmune diseases [34].

BMI is a tool to specify an individual's body fat percentage in a clinical setting. The National Institute of Health (NIH) considers three categories of BMI: less than 25 kg/m^2 signifies an average weight, 25–30 kg/m^2 indicates overweight, and over 30 kg/m^2 represents obesity [35, 36]. In our study 34 (42.6%) of patients with systemic vasculitides, obesity of varying degrees was recorded.

Depending on the type of vasculitis, various organ systems can be involved in the pathological process. The musculoskeletal system, gastrointestinal tract, skin, and cardiovascular system were most frequently affected in patients. The obtained data are similar to the results of previous studies [10, 37, 38].

Limitations

This was a retrospective and single-centre study. The number of recorded cases is small.

Conclusion

Our study revealed that the musculoskeletal system, skin, gastrointestinal tract, and cardiovascular system are frequently affected by systemic vasculitides. Most patients present with comorbidities. A sizeable portion of patients report abortions in their past medical histories. More research is warranted to better understand the pathophysiology and optimize the diagnosis and treatment of vasculitides.

Author contributions Both authors substantively contributed to the design, execution, and reporting of the study. They take full responsibility for all aspects of the study and writing.

Data availability Data are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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Clinical Rheumatology
https://doi.org/10.1007/s10067-022-06452-0

BRIEF REPORT

Physicians' perceptions about antineutrophil cytoplasmic antibody-associated vasculitis: an online survey report in the time of the COVID-19 pandemic

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Received: 3 August 2022 / Revised: 10 November 2022 / Accepted: 11 November 2022

Abstract

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are characterized by necrotizing inflammation of small and medium-size vessels that often manifest with devastating multi-organ effects. They present with a myriad of systemic features and require potent immunosuppression. Since they are uncommonly encountered in clinical practice, it is necessary to understand physicians' knowledge and perceptions about this group of diseases. An online questionnaire was designed featuring 28 questions based on relevant global practice guidelines, recommendations, and previous online surveys on AAV. The questionnaire was validated by a core group of specialists with an interest in AAV. It was shared via social networking sites and entries were restricted to physicians. Only completed entries were analyzed with descriptive statistics. A total of 113 respondents from 21 different countries responded of whom the commonest were rheumatologists, internists, and general practitioners. Forty-five (40%) ran clinics dedicated to AAV patients as a part of their practice. They commented on organs involved in AAV; vasculitis secondary to infections, drugs or other rheumatic diseases; various tests useful for AAV diagnosis; and drug choices for induction and maintenance. They mentioned their experience regarding COVID-19 in AAV patients as well as vasculitic manifestations of COVID-19. Various methods to mitigate cardiovascular risks in AAV were mentioned. Finally, the respondents indicated how medical education needed to be strengthened to increase awareness and knowledge regarding AAV. This survey helped to inform about various perceptions regarding AAV across countries, including current practices and recent evolution of management. It also provided information on treatment of the COVID-19 in AAV patients. This survey showed that there is still a lack in understanding the prevalent definitions and there is gap between guidelines and current practice.

Key Points

- *Perception about ANCA-associated vasculitis differ across countries.*
- *The number of cases encountered across 21 different countries are limited implying a need for multi-national cooperation to study this disease further.*
- *The COVID-19 pandemic has changed the approach towards ANCA-associated vasculitis by the various clinicians.*

Keywords Anti-neutrophilic cytoplasmic antibodies · Cardiovascular risks · COVID-19 · Eosinophilic GPA · Granulomatosis with polyangiitis · Microscopic granulomatosis

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides refer to a cluster of small and medium size vasculitides that are characterized by their associations with ANCA and an entire spectrum of manifestations including arthritis, hematological manifestations, pauci-immune glomerulonephritis, sinusitis, scleritis, mononeuritis multiplex, and other multi-organ manifestations. These include

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Published online: 21 November 2022

granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), and microscopic polyangiitis (MPA) [1]. An alternative classification is based on the presence of autoantibodies that may be a better predictor of disease progression [2]. Although the pathophysiology of these diseases is still under exploration, data from a few studies suggest an interrelationship between levels of anti-PR3-ANCA, HLA-DP, PRTN3, and anti-MPO ANCA [3]. The clinical presentation of ANCA-associated vasculitides (AAV) is extensive due to which the patient can present with varied manifestations, ranging from skin rashes, and epistaxis, to the involvement of the respiratory and renal tract [4]. The treatment objective of AAV is to achieve remission and avoid organ damage. A standardized definition of remission has been defined by the European Vasculitis Society/European League Against Rheumatism (EUVAS/EULAR) group [5]. It remains one of the most difficult rheumatological disorders to diagnose and treat [6].

With the evolution of better classification criteria, more and more cases of ANCA are being reported from all over the world [7]. The therapeutics and care of patients with AAV have progressed substantially in recent decades, with a corresponding improvement in overall survival [5, 8]. In addition, the ongoing COVID-19 pandemic presents a distinctive therapeutic problem for the care of patients with rheumatic diseases [9]. COVID-19 has emanated catastrophic global effects, overburdened healthcare systems worldwide, undulating effects on economies and resulted in more than six million deaths [10]. There is already a lack of detailed information from regional rheumatological societies due to the ongoing pandemic. Recently, a few case reports have linked AAV with COVID-19 [11–14]. Also, the COVID-19 pandemic has drastically affected the management of these diseases [15].

Global practice guidelines, recommendations, and perceptions of AAV require continued investigations. Along with the recommendations about what needs to be done, there should be periodic assessment on what is actually being done by clinicians. This study aims to assess and understand physicians' knowledge and perceptions of ANCA-associated vasculitis diagnosis and management with special attention to the strategy in the time of the COVID-19 pandemic.

Methods

The survey was designed to examine medical specialists' knowledge and perceptions of ANCA-associated vasculitis diagnosis and management with the intent to cover (1) global practice guidelines, (2) recommendations, (3) knowledge and experience as healthcare professionals undergoing life-long education, and diagnosing and managing patients with ANCA-associated vasculitis. The questionnaire featured 28 questions, most of which were multiple choice questions needing a single answer option (13), while others (12) could have more than one answer option selected, and some (3) needed a single answer to be selected from a list. Six items identified the respondent characteristics, and the rest covered various domains listed above.

This questionnaire was designed based on relevant global practice guidelines, recommendations, and previous online surveys on ANCA-associated vasculitis. It was validated by a core group of rheumatologists dealing with AAV. These rheumatologists checked the face validity, internal validity and reliability of the questionnaire. After finalizing, it was made available as an online form on surveymonkey.com and the link was shared via social media platforms including Twitter, Facebook, LinkedIn, and Instagram via the personal accounts of the authors. They were also encouraged to share the invitation with colleagues. There were no offline announcements and no incentives were offered. Thus, it was convenient, open sampling. The opening and closing dates for the survey were October 15, 2021 and February 15, 2022, respectively. The authors adhered to previously publicized recommendations on reporting online surveys in the time of the COVID-19 pandemic [16] as well as the Checklist for Reporting Results of Internet E-Surveys (CHERRIES).

Duplicate entries were avoided by allowing only one entry for a unique email ID. The surveymonkey.com has intrinsic checks and was configured not to accept entries without the email at the beginning. Since this was more robust than using IP checks or cookies, the latter was not used. Email IDs were not downloadable from the data collection website, ensuring anonymity of responses. There was no exclusion based on the time stamps of the surveys nor any missing data imputed. Entries were accepted only if filled in by a self-declared physician and had complete answers to all questions. This was ensured by the system since the selection of at least one response per question was ensured.

Since depersonalized data was collected, there were no issues related to data protection laws of any country.

Statistics

Categorical variables were presented as frequencies and proportions. Non-normal data were presented as medians with the intra-quartile range (IQR). Graphical presentation of data was preferred.

Ethics approval for the study was granted by the Institutional Ethics Committee of Sanjay Gandhi Postgraduate Institute of Medical Sciences (IEC approval number: 2021–298-IMP-EXP-44).

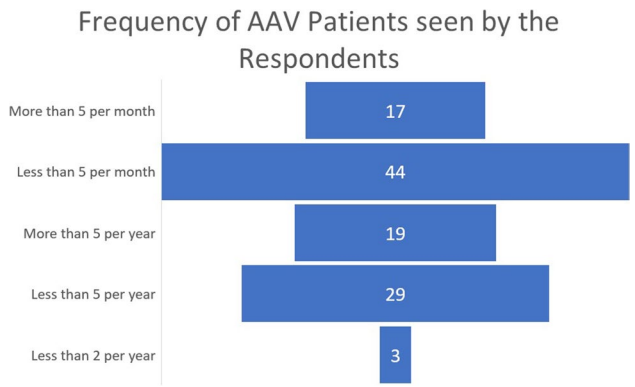

Fig. 1 Estimated number of patients with ANCA-associated vasculitis seen by the respondents

Results

There were 113 respondents with a median age of 38 (IQR: 32–45) years. Of them, 54 (51.4%) were males and 51 (48.6%) were females (8 chose not to specify their gender). The median number of years in medical practice was 13 (6–20). Most common among the responders were rheumatologists (72 [63.7%]), internal medicine specialists (14 [12.4%]), and general practitioners (8 [7.08%]). Fifty-two (46%) were from teaching hospitals while the rest worked in public clinics (30 [26.5%]), private clinics (12 [10.6%]), or both (19 [16.8%]). There were respondents from 21 different countries. The top five countries were Turkey (24), Kazakhstan (22), India (10), Ukraine (8), and Croatia (8).

Forty-five (39.8%) respondents ran dedicated clinics for the follow-up of patients with AAV 45(40%) ran clinics dedicated to AAV patients as a part of their practice. The frequency of AAV patients encountered by the respondents is presented in Fig. 1.

Knowledge about definitions and guidelines

The respondents were more conversant about the definition of AAV introduced in 2010 by the Medical Subject Headings

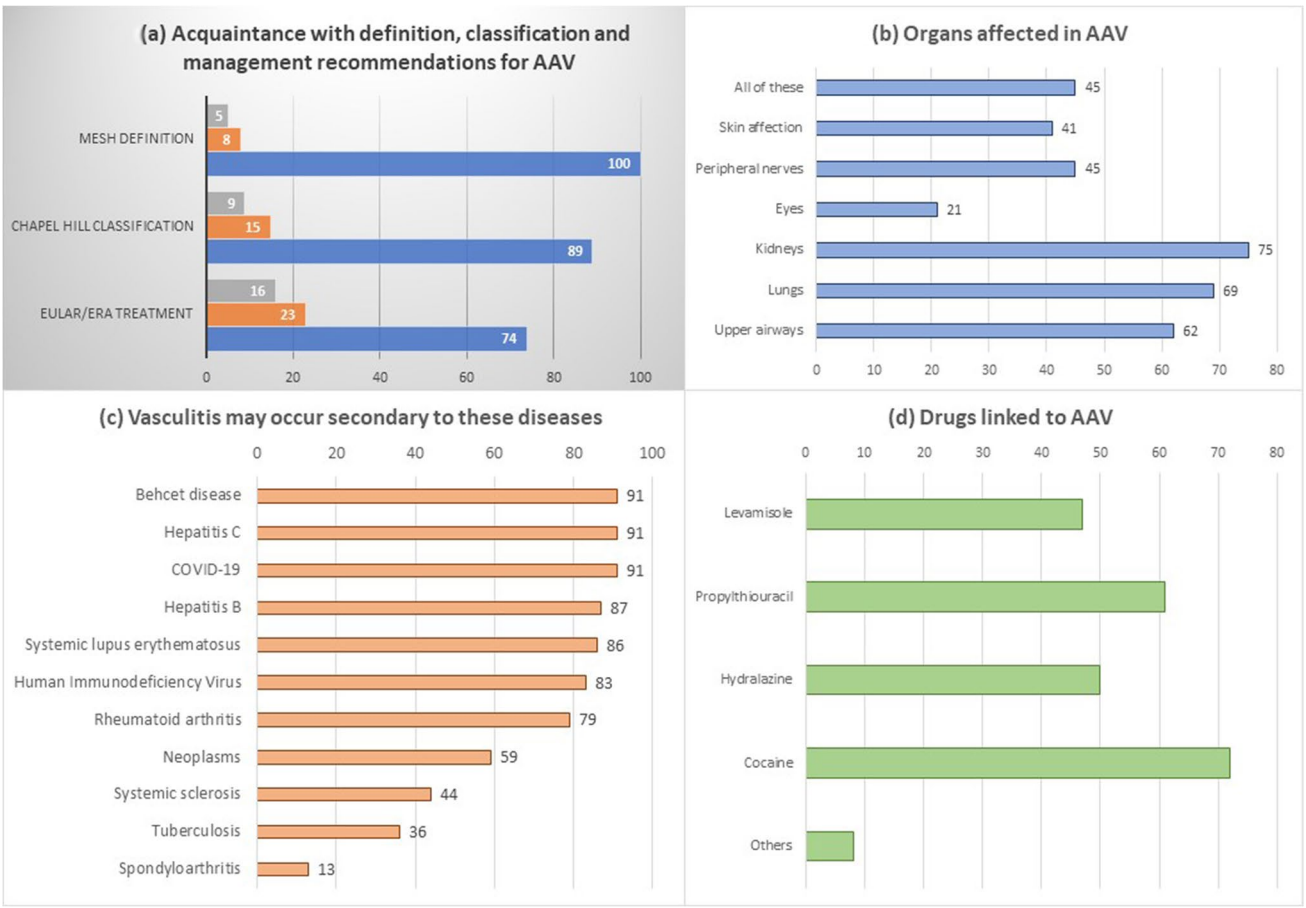

Fig. 2 **a** Respondents' acquittance with the definitions and management recommendation for ANCA-associated vasculitis. **b** organs commonly affected by ANCA-associated vasculitis. **c** Rheumatological and infectious disorders associated with secondary vasculitis. **d** Drugs associated with small vessel vasculitis mimicking ANCA-associated vasculitis.

(MeSH) of the National Library of Medicine of the United States (depicted in blue bar of 100 positive responses) than with the Chapel Hill Classification criteria or the 2016 European League Against Rheumatism (EULAR)/European Renal Association (ERA)/European Dialysis and Transplant Association (EDTA) management guidelines for AAV [Fig. 2a].

Different organs affected by AAV according to the respondents are presented in Fig. 2b. Figure 2c lists diseases associated with secondary systemic vasculitis as per the respondents while Fig. 2d summarizes drugs that can lead to small vessel vasculitis mimicking ANCA-associated vasculitis.

Choice of investigations

Table 1 summarizes investigations routinely used by respondents in the management of AAV. For determining ANCA, 69 (61.1%) preferred to test both ELISA as well as indirect immunofluorescence (IIF) while 30 (26.5%) preferred ELISA only and 14 (12.4%) were unsure. Seventy-eight (69%) respondents recommended the use of biopsy to demonstrate a granuloma for the diagnosis of AAV while 20 (17.7%) thought it was not mandatory and 15 (13.3%) were unsure.

Management and drug choices

Figure 3a shows the relative acquaintance with different recommendations related to the diagnosis, classification, and management of AAV. Figures 3b and 3c show the preferred induction and maintenance therapies, respectively. Twenty-four (21%) reported that plasmapheresis was not recommended for AAV while 29 (25.7%) and 47 (41.6%) advocated its use for pulmonary hemorrhage and rapidly progressive renal failure, respectively.

For patients who had received rituximab and had subsequent infections, 65 wanted regular monitoring of serum immunoglobulins, 18 suggested a reduction of rituximab dose, 12 preferred to discontinue it while 13 preferred to continue.

COVID-19 and AAV

Out of the 113 respondents, 54 (47.8%) had seen AAV patients who had contracted COVID-19 (diagnosed by positive RT-PCR test and/or CT chest imaging). For patients with AAV who developed COVID-19, 17 were of the opinion that corticosteroids should be titrated up; 17 wanted discontinuation of rituximab while 39 (34.5%) wanted discontinuation of all immunosuppressants except corticosteroids. Fifty-three (47%) had seen at least one patient who had had some form of vasculitis during or after recovery from COVID-19.

Cardiovascular risk management in AAV

With high disease activity leading to accelerated atherosclerosis in AAV, cardiovascular risk is a major consideration for patient management. For mitigation of CV risk, 16 (14.1%) recommended the use of antihypertensives, 22 (19.5%) antiplatelet therapy, 16 (14.1%) lipid-lowering therapy, and 86 (67.1%) all of these. Only 3 (2.7%) did not recommend any strategy for CV risk mitigation.

Medical education regarding AAV

Amongst the respondents, all wanted medical curricula to include more topics on AAV. Forty-two (37.2%) suggested augmentation of teaching regarding clinical features of vasculitis, 35 (31%) suggested including vasculitic manifestations of common inflammatory rheumatic diseases, 32 (28.3%) wanted more courses on the diagnostic value of ANCA antibodies, while only 22 (19.5%) suggested including information about thrombosis in AAV.

Discussion

This survey has summarized the knowledge and perception of an international group of physicians dealing with AAV in the COVID-19 pandemic. Although the number of

Table 1 Investigations employed by respondents in the management of AAV

Test	Preferred by
Full blood count (CBC)	95
C-reactive protein	95
Serum creatinine	93
Anti-neutrophil cytoplasmic antibodies (ANCA)	92
Urinalysis	90
Erythrocyte sedimentation rate	89
Liver function tests	78
Chest computed tomography	76
Chest X-ray	74
Hemoglobin	71
Imaging of paranasal sinuses	62
Serum albumin	61
Histopathological tests (renal/lung biopsy)	61
C3 and C4 (complement fractions)	44
Tests for HIV	41
Antinuclear antibodies (ANA)	40
Antiphospholipid antibodies	32
Cryoglobulins and cryofibrinogen	32
Rheumatoid Factor (RF)	29
Serum amyloid A (SAA)	17

respondents is relatively small, there is a wide geographic representation. AAV is a rare but life-threatening disease with a myriad of clinical features which may confuse clinicians at different levels of healthcare. The majority of the survey respondents were used to seeing less than 5 patients with AAV a month, stressing the relatively low prevalence of this disease. This may be a reason that less than 50% of the respondents could identify all the organs that can be potentially affected by AAV. As a result, clinicians may underdiagnose organ-limited AAV [17]. Also, the number of respondents who know about vasculitides secondary to drugs, infection, or autoimmune diseases is less than optimal. This is reflected in the choice of investigations. The respondents unaware of the secondary cause of vasculitides were less likely to test for ANCA antibodies and thus related diagnoses may be missed. Less than a third of respondents opted to look for cryoglobulins and cryofibrinogen, implying that these diagnoses may be frequently missed [18].

The current recommendation for testing ANCA stresses that "high quality (solid phase) immunoassays" testing is sufficient [19]. However, when such solid phase immunoassays are unavailable, it is better to augment the ELISA testing with indirect immunofluorescence testing. This was possibly reflected in the choices of the respondents. Also, serial monitoring of ANCA levels is helpful to predict relapses [20].

Regarding the management of AAV, the top choices were cyclophosphamide followed by rituximab and methotrexate which is in line with the standard recommendations [21]. Some centers today prefer rituximab as the first-line therapy but cyclophosphamide has the largest base of evidence and trials have not proven the superiority of rituximab over cyclophosphamide [22]. Similarly, for induction, the most preferred were azathioprine and rituximab. The therapeutic armamentarium against AAV is expected to increase in the near future with drugs such as avacopan already receiving regulatory approval [23].

Management of cardiovascular risk factors in rheumatic disease, especially vasculitides, is an integral part of care. There is evidence that this risk factor correlates with disease activity [24]. And early control of disease is associated with

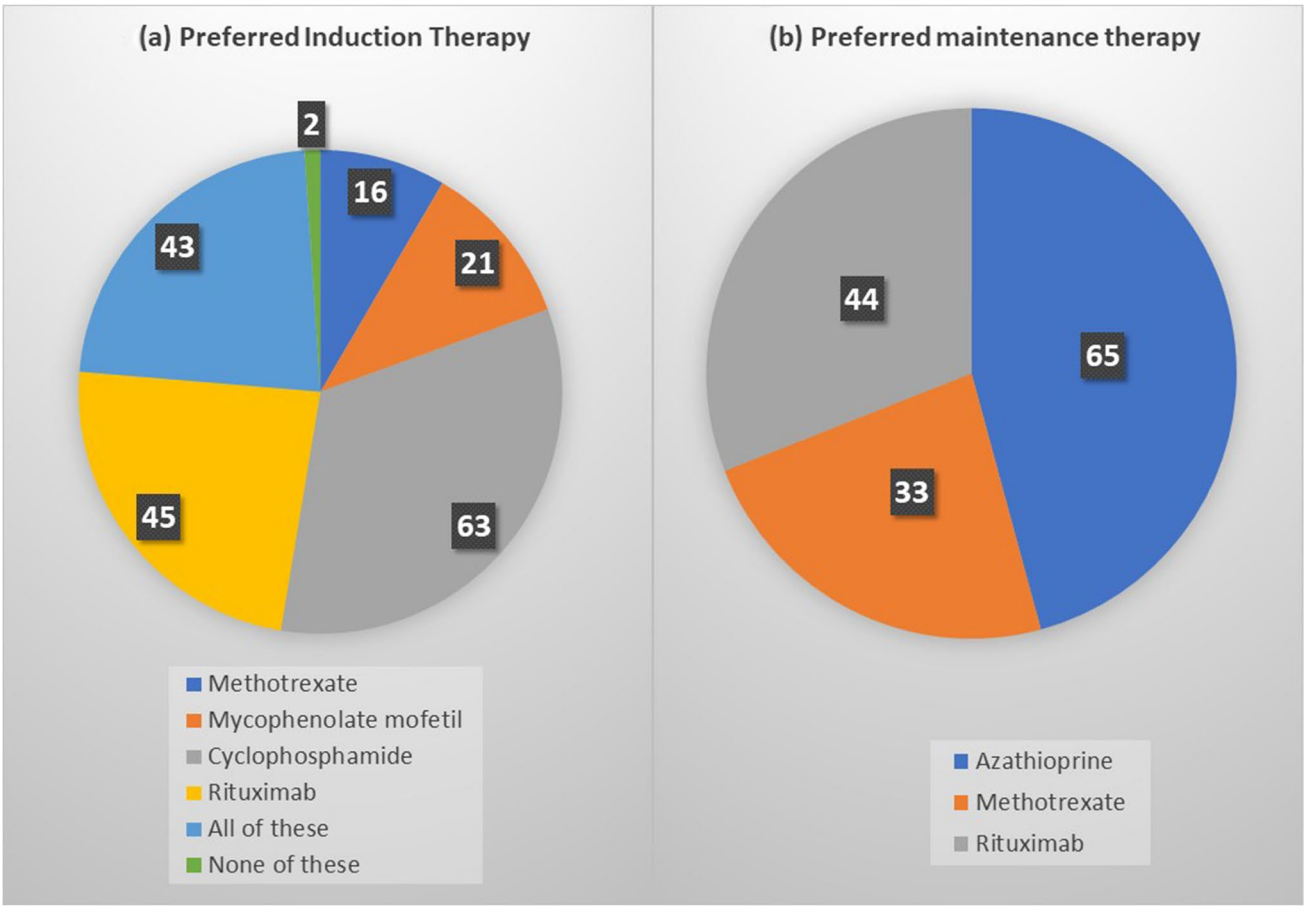

Fig. 3 **a** Drugs preferred for induction in AAV and **b** drugs preferred for maintenance of remission in AAV. Note: one respondent can choose more than 1 option as the preferred therapy.

better long-term outcomes [25]. Nevertheless, comorbidities such as metabolic syndrome are still an independent risk factor even in the presence of disease activity [26]. Thus, clinicians must always aim for aggressive disease management and should not neglect to address independent cardiovascular risk factors. Another aspect to consider is the mitigation of infection risks to reduce morbidity and mortality [27].

It was interesting to note that COVID-19 was not uncommon in patients with AAV. Most of the respondents preferred to hike up corticosteroid doses and minimize other immunosuppression during COVID-19. This may seem appropriate in the setting of an infection but it may be counter-intuitive to increase immunosuppression. However, COVID-19 can precipitate and even aggravate pre-existing rheumatic diseases. In certain scenarios, it may require higher immunosuppression also [28]. Endothelial injury and NETosis found in COVID-19 may predispose to small-vessel vasculitis such as AAV [29]. But in a clinical scenario, it is always difficult to balance the correct amount of immunosuppression and the clinicians might want to err on the side of omission rather than commission, as was evident from a previous survey on this topic [30].

This survey also brings out the need for updating knowledge and awareness about small-vessel vasculitis amongst all the medical fraternity from the foundation years onwards. The limitation of this survey is the relatively small number of respondents. Since we excluded incomplete responses, this might have further reduced the number of analyzed responses. However, AAV is an uncommon disease and the number of clinicians showing interest may be limited until greater awareness is achieved. On the other hand, the survey is representative since it included physicians from numerous countries and a good mix of rheumatologists, internal medicine specialists, immunologists, and other practitioners. Another limitation was that we could not report the response rate since it was an open survey disseminated via social media.

The survey found heterogeneity in how treating clinicians define and approach ANCA-associated vasculitis. There is a dearth of consensus regarding investigations, management during COVID-19 or management of cardiovascular risks. However, all respondents were unified in stating the need to increase education on AAV during medical training. It is an uncommon disease and easily missed. Many etiological factors such as infections and their relationship with thrombosis are poorly understood. Thus, to progress further in combatting this disease, there needs to be better education and focused research with international collaboration.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10067-022-06452-0.

Author contribution Akerke Auanassova: conceptualization, revision of the questionnaire.

Olena Zimba: drafting and revising the questionnaire.

Armen Yuri Gasparyan: responsible for organizing the survey and revising the questionnaire.

Mrudula Joshi: processing SurveyMonkey data, generating graphs, responsible for data accuracy.

Vikas Agarwal: ethics approval, revision of the questionnaire.

George D. Kitas: conceptualization of cardiovascular risk in vasculitides, editing final version of the manuscript.

Sakir Ahmed: drafting the initial version of the manuscript, revising it, and adding new concepts in the interpretation of data.

Declarations

Conflict of interest Dr. Ahmed reports honoraria as speaker from Pfizer, Dr. Reddy's, Cipla, Novartis, and Jansen, all outside the submitted work. All other authors report no conflicts of interest.

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Central Asian Journal of Medical Hypotheses and Ethics
2024; Vol 5(2)

eISSN: 2708-9800
https://doi.org/10.47316/cajmhe.2024.5.2.01

CLINICAL MEDICINE REVIEW

SYSTEMIC VASCULITIS IN KAZAKHSTAN: A COMPLEX RESEARCH APPROACH

Received: April 2, 2024
Accepted: June 20, 2024

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Abstract
Rare diseases known as systemic vasculitides involve the inflammatory destruction of blood vessels, leading to complex disorders that can affect a single organ or multiple organs and systems. The challenges in diagnosis, coupled with the lack of awareness among healthcare providers, particularly primary care physicians, and delayed treatment, often result in disability and worsen the prognosis of systemic vasculitis patients. We have conducted a comprehensive research approach to understand the features of systemic vasculitis, considering demographic, clinical, and laboratory data in Kazakhstan (Shymkent city and the Turkestan region). This approach, which encompasses a retrospective research method, an analytical research method, and a one-stage cross-examination (online survey), is essential in our quest to improve the understanding and management of systemic vasculitis in Kazakhstan.

Keywords: Vasculitis, Systemic vasculitis, Survey, Questionnaire, COVID-19
How to cite: Auanassova A. Systemic vasculitis in Kazakhstan: a complex research approach. Cent Asian J Med Hypotheses Ethics 2024:5(2):87-92. https://doi.org/10.47316/cajmhe.2024.5.12.01

INTRODUCTION
Rare illnesses known as systemic vasculitides (SV) involve the inflammatory damage of blood vessels, leading to complicated conditions that can affect a single organ or multiple organs and systems [1]. The Chapel Hill Consensus Conference (CHCC) established a system for categorising SV in 1994. Two decades later, they updated the naming system to include more categories and reflect current trends and advancements in understanding vasculitis [2,3]. SV can be classified by the vessel sizes primarily involved (large, medium, small), clinical presentations, root causes, or histological characteristics [1,4]. These conditions impact patients of every age group and present distinctive difficulties in diagnosis and treatment [5].

Over the last four decades, improved drug regimens have changed vasculitis from an often lethal, sudden illness to a continuing disorder with recurring episodes and lasting effects that many patients live with for a long time [6]. Most SV have no universal test or specific diagnostic guidelines [7]. The outlook for SV is no longer always deadly, but individuals may still have ongoing symptoms, permanent damage to their organs, and adverse effects from immunosuppressive therapy [8,9]. It has been reported in the literature that 25% of individuals with primary vasculitis suffer from depression, while over 40% experience anxiety [10]. Approximately 25% of individuals with ANCA-associated vasculitis (AAV) are unemployed, and 50% have expressed that their condition hinders their professional advancement [11,12].

Thus, the following goal was established for a more in-depth investigation of SV, an autoimmune condition of significant importance in Kazakhstan and globally. Considering clinical and laboratory data, the dissertation research aimed to optimise treatment tactics and identify patients with SV in Shymkent City and the Turkestan region.

To achieve this goal, the following tasks were set:

1. To analyse systemic vasculitis that first appeared after infection with COVID-19 and vaccination;
2. To evaluate the factors leading to delayed diagnosis of systemic vasculitis;
3. To study the demographic, clinical and anamnestic features of individuals with SV in the period from 2019 to 2021;
4. Evaluating the understanding and attitudes of healthcare professionals in the Republic of Kazakhstan and abroad regarding systemic vasculitis;
5. To provide recommendations for improving the management approach for patients with systemic vasculitis.

A complex research approach was applied to achieve the research goal and solve each task.

The study coincided with the COVID-19 pandemic, so choosing a retrospective research method and an online survey of healthcare professionals (a cross-sectional study) was advisable.

Millions of fatalities worldwide have resulted from COVID-19. The disease's widespread transmission was primarily due to respiratory issues being the most prevalent symptoms [13]. During the early stages of the pandemic, steps like isolation, maintaining physical distance, quickly tracing patients, limiting access to enclosed spaces, and reducing crowding were implemented to handle the transmission of the illness [14].

In 2020, the COVID-19 pandemic energised the international scientific society, especially in life sciences [15,16]. The pandemic altered numerous facets of human existence worldwide, leading to enduring adverse social and economic repercussions [17,18].

In the first phases of the study, and when gathering patient data, extensive examination of the data linked to the selected subject was conducted.

A literature review involves a thorough and critical examination and integration of the current research and academic literature concerning a particular subject. It summarises the present understanding, concepts, and discussions related to the topic, ultimately laying the groundwork for the research carried out in the dissertation or thesis. A literature review is critical in contextualising research by offering a thorough overview. It tracks the development of concepts, theories, and research results in the field, preparing the groundwork for your investigation. Through analysing existing literature, researchers can grasp the present knowledge landscape, pinpoint essential topics, and examine how their research adds to the larger academic discourse.

Researchers use the literature review to help them choose the proper methodologies for their study. By looking at how previous studies were carried out, what methods were used, and which approaches were successful, researchers can learn about the best practices and potential problems in research design. This information helps researchers decide about data collection, analysis techniques, sampling methods, and overall research strategy. The literature review provides a framework for selecting research methods and allows researchers implement reliable and feasible research methods that align with standard practices in the field [19].

Also, before the start of the study, the ethical approval of the Local Ethics Commission was obtained, where all relevant documents related to the planned research were provided (research protocol, form of informed consent of the subjects, abstract of the work, questionnaire questions, etc.).

LITERATURE REVIEW

Literature data show that COVID-19 infection and COVID-19 vaccines can cause SV, similar to the phenotypes of primary vasculitis. IgA vasculitis and leukoclastic skin vasculitis are the most common vasculitis reported after infection or vaccination with COVID-19, with a better prognosis than de novo vasculitis [20,21]. Steroids play a central role in treatment, and in most reported cases, a positive effect of prednisone doses of 0.8 to 1 mg/kg per day was observed. Vasculitis that develops after coronavirus infection damages blood vessels of all sizes, and therefore, it was recommended that they be classified as «Virus-specific vasculitis» in the Chapel Hill consensus [21].

During the assessment of the factors leading to the delay in the diagnosis of SV, it was concluded that the relatively low level of SV and insufficient awareness of general practitioners, as well as the uneven clinical signs of SV, suggest a delay in diagnosis. Increasing the awareness of therapists and providing patients with timely access to rheumatological care ensures the initiation of timely treatment, which leads to a reduction in injuries caused by SV and an improvement in the quality of life. Raising the public's and doctors' awareness about detecting systemic vasculitis early and establishing efficient referral systems is crucial. Achieving this necessitates the involvement and agreement of all stakeholders, including rheumatologists, diverse medical communities, and politicians [22].

At this stage, we conducted a comprehensive, thorough literature review, which allowed us to examine what had been studied before, identify gaps in our research area, and, most importantly, build a highly accurate research plan [23].

A RETROSPECTIVE STUDY OF PATIENT MEDICAL HISTORIES

The virus that causes COVID-19 rapidly spread across the globe and was characterised as a pandemic by the WHO on March 11, 2020. Local and national recommendations implemented the following public health measures, including the extensive adoption of masks and the observance of social distancing. Schools and businesses were temporarily shut down, big events were limited, and individuals were encouraged to stay away from others to prevent the virus from spreading [24].

According to the tasks set, it was necessary to analyse the medical history data of patients with systemic vasculitis from 2019 to 2021 and study their demographic, clinical, and anamnestic characteristics. To accomplish this task, it was advisable to choose a retrospective research method since the study period coincided with the COVID-19 pandemic, and difficulties arose with patient access.

An analysis of the demographic, clinical, and historical traits of patients with systemic vasculitis in the years 2019, 2020, and 2021 revealed that the condition was most commonly diagnosed in female patients within the studied group (Shymkent city and Turkestan region). The most prevalent conditions were Takayasu disease (43.9%) and IgA vasculitis (31.71%). Patients had a range of health issues, including diabetes, anaemia, coronary heart disease, high blood pressure, and gastrointestinal tract conditions. In the analyzed groups, 27.1% of the individuals exhibit some form of disability, and most of these individuals fall into the category of group II disability. Out of 162 patients, the obesity rate is 37.6%. The musculoskeletal system was affected in 75.6% of patients with systemic vasculitis, while the gastrointestinal tract was affected in 57.3%. Additionally, the skin was impacted in 48.8% of patients, and peripheral vessels were affected in 37.8% of cases. Finally, the cardiovascular system showed symptoms in 31.7% of patients [25,26].

At this stage, we have revealed that most patients in the studied population are women of reproductive age of rural origin. The patient's profound level of disability is a reminder of the consequences of delayed treatment and the absence of comprehensive information about managing systemic vasculitis in the medical community. This situation has caused a pattern of delayed diagnosis and treatment. The significance of doctors' in-depth knowledge about autoimmune diseases cannot be overstated. It is essential to quickly and promptly identify these conditions and refer the patient to a rheumatologist. The rheumatologist has a vital function in the treatment process and in ensuring the application of appropriate treatment. This is vital for achieving positive patient outcomes and a favourable prognosis.

ONLINE SURVEY DURING THE COVID-19 PANDEMIC: A ONE-STEP CROSS-SECTIONAL STUDY

Survey research is vital in the healthcare field. It gathers information about healthcare delivery, service utilisation, and general issues related to the quality of care [27].

Over the last twenty years, online surveys have become necessary as a significant research methodology [28]. The benefits of online surveys have become increasingly clear amidst the COVID-19 pandemic. The frequency and rapid publication of online surveys over the past half-year evidence this [29].

According to the task, an online survey (a one-step cross-sectional study) of healthcare professionals in Kazakhstan and abroad was conducted. During the COVID-19 pandemic, the research was carried out when it was not feasible to conduct face-to-face interviews with physicians; using this approach was the most efficient and saved time.

A web-based questionnaire connected demographic segments in various regions of the world [30].
The survey included 113 healthcare professionals from 21 nations, such as rheumatologists, internists, and general practitioners. Respondents shared information

on organs affected by AAV, vasculitis causes, diagnostic tests, medication options, and the impact of COVID-19 on AAV patients.

The information gathered in this study reflects the understanding and viewpoints of a global team of medical professionals managing AAV during the COVID-19 outbreak.

This questionnaire mainly focused on clinical aspects: knowledge of definitions and guidelines, choice of diagnostic methods, management of cardiovascular risks in AAV, medical education regarding AAV, patient management and drug selection, and COVID-19 and AAV.

The survey has shown that all medical professionals must refresh their awareness about small vessel vasculitis from its early development stages.

The survey also highlighted various approaches to reducing cardiovascular risks in AAV and emphasised the importance of improved medical education to enhance awareness and knowledge about AAV [31].

Results from an internet-based healthcare practitioner questionnaire indicated differences in AAV identification and management. The questionnaire showed a need for more consensus on managing AAV patients during the COVID-19 pandemic.

GUIDANCE FOR THE MANAGING OF SYSTEMIC VASCULITIS DURING CORONAVIRUS INFECTION AND AFTER VACCINATION AGAINST COVID-19

As part of the fifth task, «Recommendations for managing systemic vasculitis during COVID-19 and after vaccination against COVID-19» were developed.

At the initial stage of the study, a comprehensive analysis of the existing literature revealed that there is no single algorithm for managing patients with SV during coronavirus infection and after COVID-19 vaccination.

The recommendations are based on the recommendations of EULAR and ACR, as well as recent literature data and the results of individual studies, to provide medical professionals with up-to-date information on treating systemic vasculitis during and after vaccination against COVID-19. The guidelines have been developed as a guide for medical professionals providing medical care to patients with autoimmune rheumatological diseases, students of medical universities, and residents.

CONCLUSION

To summarise, the types and features of systemic vasculitis, which are most common among the adult population in modern conditions, depending on gender, age, and socio-demographic characteristics in the Republic of Kazakhstan (using the example of Shymkent city and Turkestan region) (2019-2021), were presented, which had not been studied before.

Of particular importance is increasing the awareness and literacy of primary care physicians, general practitioners and rheumatologists regarding the timely diagnosis of systemic vasculitis and improving the prognosis of patients' lives.

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ҚАЗАҚСТАНДАҒЫ ЖҮЙЕЛІ ВАСКУЛИТТЕР: КЕШЕНДІ ЗЕРТТЕУ ТӘСІЛДЕРІ

Түйін

Жүйелі васкулиттер деп аталатын сирек кездесетін аурулар қан тамырларының қабынуымен бірге жүретін бұзылуын қамтиды, ауру тобы бір мүшеге немесе бірнеше мүшелер мен жүйелерге әсер етуі мүмкін күрделі бұзылыстарға алып келеді. Диагностика жасаудағы қиындықтар, медицина қызметкерлерінің, әсіресе алғашқы медициналық көмек дәрігерлерінің хабардар болмауынан және емнің кешіктірілуі салдарынын көбінесе мүгедектікке алып келеді және жүйелі васкулитпен ауыратын науқастардың өмір сүру болжамын нашарлатады. Біз Қазақстандағы (Шымкент қ. және Түркістан облысы) демографиялық, клиникалық және зертханалық мәліметтерді ескере отырып, жүйелі васкулиттердің ерекшеліктерін түсіну үшін кешенді зерттеу әдісін жүргіздік. Ретроспективті, аналитикалық және бір сатылы кросс-тексеру (онлайн- сауалнама) сынды зерттеу әдістерін қамтитын бұл кешенді зерттеу Қазақстандағы жүйелі васкулиттерді түсіну мен басқаруды жақсартуға ұмтылуымызда өте маңызды.

Түйінді сөздер: васкулит, жүйелі васкулиттер, сауалнама, COVID-19.

Дәйексөз үшін: Ауанасова А. Қазақстандағы жүйелі васкулиттер: кешенді зерттеу тәсілдері. Орта Азиялық медицина гипотезасы мен этикасы журналы 2024:5(2):87-92. https://doi.org/10.47316/cajmhe.2024.5.2.01

СИСТЕМНЫЕ ВАСКУЛИТЫ В КАЗАХСТАНЕ: КОМПЛЕКСНЫЙ ПОДХОД ИССЛЕДОВАНИЯ

Резюме

Редкие заболевания, известные как системные васкулиты, включают воспалительное разрушение кровеносных сосудов, приводящее к сложным нарушениям, которые могут поражать один орган или несколько органов и систем. Проблемы в диагностике в сочетании с недостаточной осведомленностью медицинских работников, особенно врачей первичной медико-санитарной помощи, и задержкой лечения часто приводят к инвалидности и ухудшают прогноз пациентов с системным васкулитом. Мы провели комплексное исследование для понимания особенностей системных васкулитов с учетом демографических, клинических и лабораторных данных в Казахстане (г. Шымкент и Туркестанская область). Этот подход, который включает в себя метод ретроспективного исследования, метод аналитического исследования и одноэтапный перекрестный опрос (онлайн- опрос), имеет важное значение в нашем стремлении улучшить понимание и лечение системных васкулитов в Казахстане.

Ключевые слова: васкулит, системные васкулиты, анкетирование, COVID-19.

Для цитирования: Ауанасова А. Системные васкулиты в Казахстане: комплексный подход исследования. Центральноазиатский журнал медицинских гипотез и этики 2024:5(2):87-92. https://doi.org/10.47316/cajmhe.2024.5.2.01