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MEDICINE

Untypical Manifestations of Granulomatosis with Polyangiitis—A Review of the Literature

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Abstract

Granulomatosis with polyangiitis (GPA, previously known as Wegener's granulomatosis) is a type of ANCA-associated vasculitis that affects small- to medium-sized vessels. GPA occurs with a prevalence of 24–152:1000000. The disease affects all races at every age. Various factors may have an impact on the etiology of GPA which is treated as an autoimmune disease. Genetic factors, infectious agents (like *Staphylococcus aureus*), environmental factors (like silica, hydrocarbons, fumes, pesticides, and farming) are considered elements for the development of the disease. Mostly, GPA affects the upper and lower respiratory tracts and kidneys and associated with otorhinolaryngological and renal manifestations. However, numerous untypical manifestations may also occur. Our review is aimed at discussing the most significant of them, including the neurological, cardiac, gastrointestinal tract, joints and muscles, skin, and ophthalmological manifestations. The whole literature was searched in PubMed. It has been used phrases granulomatosis with polyangiitis', Wegener's granulomatosis' and GPA'. The initial research for every sentence yielded subsequently, 4472, 5043, and 7110 results. Only studies with available full text were retrieved. After a three-stage evaluation including a language evaluation, a heading evaluation, and an abstract evaluation, we obtained 139 relevant papers on which our review is based. GPA is a huge challenge for contemporary diagnostics and medicine. Our review is aimed at demonstrating the multiplicity of untypical manifestations and proving that every doctor may come into contact with a patient with GPA.

Keywords Granulomatosis with polyangiitis · GPA · Central nervous system · Untypical manifestations · Skin

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Background

Granulomatosis with polyangiitis is an autoimmune disease presenting with various symptoms and signs. This multiplicity of manifestations may be misleading and, in consequence, delays establishment of proper diagnosis and treatment. We would like to present a literature review providing untypical manifestations of GPA.

We searched PubMed with the phrases, granulomatosis polyangiitis', GPA', and Wegener's granulomatosis' and with each of the preceding phrases appended with each of the following additions nervous system', heart', gastrointestinal tract', joints', muscles', skin' and eyes' (e.g. granulomatosis polyangiitis nervous system', granulomatosis polyangiitis heart'). Only articles with available abstracts and full text were considered. For related titles, the abstracts were reviewed and, if still appropriate, the articles were added to our work in full version. References within the selected articles were also reviewed and accepted depending on their accuracy. Ultimately, we used 139 articles in our work.

Introduction

Granulomatosis with polyangiitis (GPA, previously known as Wegener's granulomatosis) affects small-sized to medium-sized vessels causing vasculitis [1, 2]. Vessels of the upper or lower airways or whole respiratory tract and kidneys are involved with a prevalence of 90% [3] and 78% [4], respectively. The biopsy findings include neutrophilic vasculitis with necrosis and multinucleated giant cells and mononuclear infiltrate in walls of vessels affected with fibrinoid necrosis [5, 6].

GPA occurs with a prevalence from 24 to 152:1000000 [7–13]. Interestingly, the frequency of its prevalence depends on geographic position [14], for example, there is a greater frequency in the north of Europe. The disease affects all races. However, Caucasians are mostly affected [1]. An age-specific peak depends on a study. Some authors observed the highest tendency between 55 and 64 years [15] and others between 45 and 60 years [16]. But GPA can occur among patients at every age [17].

GPA is a type of ANCA-associated vasculitis. ANCA are antineutrophil cytoplasmic autoantibodies and can be directed against the neutrophil serine proteinase-3 (PR3-cANCA) and against the neutrophil enzyme myeloperoxidase (MPO) [18]. A positive result for these types of antibodies may be obtained for about 70–80% and 10% of patients respectively [19]. The diagnostic criteria were not distinguished. The American College of Rheumatology established the following classification criteria for GPA: (1) abnormal urinary sediment, (2) abnormal findings on chest radiograph, (3) oral ulcers or nasal discharge, and (4) granulomatous inflammation on biopsy [20]. Clinical picture suggesting a vasculitis accompanied by a positive ANCA test and a positive biopsy result showing evidence of necrotizing vasculitis, necrotizing glomerulonephritis, or granulomatous inflammation suggests strongly a diagnosis of GPA [21].

Various factors may have an impact on the etiology of GPA which is treated as an autoimmune disease [22]. Genetic factors [23], infectious agents (like *Staphylococcus aureus* [24]), environmental factors (like silica [24], hydrocarbons [25], fumes [26], pesticides [26], and farming [27]) are considered elements for the development of GPA.

GPA is known as a disease affecting the upper and lower respiratory tracts and kidneys and associated with otorhinolaryngological and renal manifestations. But it does not mean that GPA is limited only to these organs. Vessels, for example, in the heart, skin, eyes, muscles, gastrointestinal tract, and breast may be involved as well [28, 29].

The mortality of untreated GPA is high, so the issue of effective treatment is vital. EULAR recommends assigning patients with GPA to different levels of severity to allow for adjusted treatment [30] which consists of two phases: the induction phase and the maintenance phase. The first phase is aimed at inducing the remission [16, 31]. EULAR recommends a combination of cyclophosphamide (intravenous or oral) and prednisolone [30]. The above therapy will be preceded by an intravenous bolus of methylprednisolone, if the disease is refractory or severe and the cardiovascular patient's condition allows for it. The boli can be administered once daily for 3 days. Once the proper time of treatment has elapsed, the dose of oral prednisolone should be gradually reduced [16]. Immunosuppressive agents like cyclophosphamide play important roles, but cause side effects [32] (infections, bone marrow suppression, cystitis [33]) and is toxic. EULAR recommends antiemetic therapy if cyclophosphamide is intravenous. The patient should drink a lot of fluid to prevent the concentration of harmful substances in urine. However, if contraindications exist, then cyclophosphamide can be swapped for methotrexate, but not in organ-threatening or life-threatening forms. In early systemic GPA, the patient can be treated with methotrexate. It is advantageous to administer folic or folinic acid during methotrexate therapy [30]. Rituximab is effective as an immunosuppressive agent, so it can be used as an alternative for cyclophosphamide [16, 33]. In the second phase, EULAR also recommends a combined therapy. The maintenance treatment consists of low-dose glucocorticoids and either azathioprine, leflunomide, or methotrexate. The second phase should persist at least 18 months [30]. Refractory cases are treated with rituximab, TNF-α antagonists, intravenous immunoglobulin, deoxyspergualin, and anti-thymocyte globulin [32]. Plasma exchange is used in selected cases with rapidly progressive renal disease [30] and only additionally to prescribed therapy [33]. However, its effectiveness has not been well studied [30, 33].

Neurological Involvement

Neurological involvement was observed in 22 to 54% [34–37] of patients with GPA. The results received before the use of an adequate therapy were the highest. Later researches indicate smaller prevalence [37]. The changes are not only an effect of vasculitis, because the granulomatous lesions can spread from their adjacent primary places like the nasal cavity, paranasal sinuses, and orbit and involve the optic nerve, optic chiasm, pituitary gland, nasal vestibule, base of the brain, and meninges [38]. The entanglement of lower cranial nerves and meninges may come from a spreading contiguous primary granulomatous lesion located in the middle ear [36]. Moreover, a granulomatous lesion remote from nasal granulomas can affect meninges, cranial nerves, the brain, and parietal bone. According to the results of one study which distinguished these three possible pathogenic processes, vasculitis occurred in 28% of patients, granulomatous lesions spreading through the walls of the nasal cavity occurred in 26% of patients, while remote granulomatous formations affecting cranial and cerebral structures concerned only 4% [38].

Neurological involvement can be divided into peripheral nervous system involvement with a prevalence of between 10.6 and 43.8% [3, 35, 37, 39–42] and into central nervous system involvement affecting 2–11% of patients [3, 37, 41–43]. Vasculitis underlies peripheral neuropathy [38]. The median time from the beginning of GPA to neuropathy is 8.4 months [35]. The spectrum of changes in the nervous system includes various signs and symptoms. Patients complain of paresthesia, numbness, burning pain, and paresis whereas, there is a group which does not display any symptoms (18%). Their diagnosis of the peripheral nervous system involvement is based on clinical and electrophysiologic tests. The impairment of touch sensation and absence of tendon reflexes are the most common findings (respectively 66% and 50%). Other clinical findings include impairment of pain sensation, vibration sensation, temperature sensation, paresis, and muscular atrophy. These ailments can be the result of axonal neuropathy (definitely more often) or demyelinating neuropathy. It is possible for both of these two lesions to occur at the same time [42]. A large study done by Nishino et al. showed that the most common peripheral neuropathy is multiple mononeuropathy with a prevalence of 80% in patients with peripheral nervous system involvement. In this paper, the damages concerned the peroneal, tibial, ulnar, median, radial, and femoral nerves. Distal symmetrical sensorimotor polyneuropathy occurs in 11% of cases with peripheral neuropathy [35]. In contrast to the frequencies of types of neuropathy, another paper states that symmetrical sensorimotor polyneuropathy befalls patients slightly more frequently (55%), whereas mononeuropathy happens in 45% of cases. According to the results of this study, similar nerves are affected. Changes in the peroneal nerve are the most common [42]. Renal involvement is observed significantly more often among patients with polyneuropathy [35]. Moreover, these patients have a greater extent of disease and higher ANCA titer than those without polyneuropathy [42].

Cranial nerve involvement occurs in 4.7–9% of patients with GPA [35, 37, 42]. According to a study by Nishino et al., the most frequently affected cranial nerve is the optic nerve (48% of patients with cranial nerve manifestation, 3% of patients with GPA) [35]. Every cranial nerve can be affected [35, 44, 45]. Neuropathy of the sixth or seventh nerve occurs quite often as can be evidenced by the fact that it affects 38% of patients with cranial nerve manifestations (2.5% of patients with GPA) [35]. Adjacent orbital granuloma is the most common cause for compression of the second nerve, leading to its eventual atrophy [44, 46]. Optic neuritis is a rare condition caused by GPA [34]. Facial nerve palsy is often related to involvement of the middle ear [47, 48] due to the close anatomical proximity of these structures [44]. Various authors have announced unilateral and bilateral cranial nerve manifestations [34, 35, 49]. In the literature, there are described cases of patients who suffered from palsies of all the cranial nerves apart from the first, fifth, and seventh nerves [50].

Central nervous system involvement includes three clinical categories: hypertrophic pachymeningitis, pituitary gland involvement, and cerebral vasculitis [43]. Meningitis generally occurs more frequently among patients with the limited form of GPA. About 70% (70.3%) of cases with meningeal involvement concern patients with the localized type whereas only 10.8% and 18.9% involve patients with early systemic disease and the generalized form, respectively. The most probable reasons for such discrepancy are the easier spreading of and involvement of meninges with a granulomatous lesion in the upper respiratory tract [51]. But it should be remembered that this condition occurred with a prevalence of 0.6% in a large cohort study (324 patients) [35, 51]. The most common symptom in chronic meningitis is headache which is not a specific symptom and impedes establishment of proper diagnosis. Other neurological abnormalities generally develop during the later course of GPA development. Brain meninges are affected more frequently than spinal meninges (87.5% vs 14.6%). The difference between the frequencies of abnormalities concerns the types of meninges as well (changes in the dura mater equal 81.2% while changes in the leptomeninges amount to 27.1%). Among patients with spinal cord meningitis, the patients complain of neck or back pain. But spastic paresis may occur too [51]. MRI (magnetic resonance imaging) shows bilateral diffuse symmetric linear dural thickening and enhancement but focal findings and nodular thickening are described as well [38]. A diffuse pattern of thickening was found significantly often (72.9%) [51]. Laboratory tests show pleocytosis with dominance of leukocytes and elevated protein concentration as a coexisting or single sign [43]. Necrotizing granulomatous inflammation was the main finding (61.5%) in meningeal biopsies. Other pathologic features, which were found in samples, were described as small vessel vasculitis, coexisting granulomatosis and vasculitis, lymphocytic inflammation, and fibrous thickening [51].

Another rare manifestation of central nervous system involvement is involvement of the pituitary gland. According to Hoffman et al. results, it occurs in 0.6% of patients with GPA [3]. In a large study, the prevalence is a little higher (1.3%) [52]. Patients present with nonspecific symptoms: headache, asthenia, vomiting, and muscular atrophy. Muscular atrophy may be induced by taking glucocorticosteroids [53]. Visual disorders, like bitemporal hemianopsia, are observed in 17% to even 40% of cases [43, 52]. Posterior lobe insufficiency resulting in diabetes insipidus is the most common disorder among patients with pituitary involvement [43, 53] and concerns 71% of cases [53]. Diabetes insipidus responds to vasopressin injections [43]. Reviewing the literature, it can be found that gonadotropin deficiency occurs in 45% of patients [53]. In some studies, the frequency of this condition was much higher (78% [53] and 87.5% [52]). The prevalence of hypogonadism in GPA may be underestimated because gonadotropin secretion is connected with drugs

(glucocorticosteroids), acute illness, malnutrition, and hyperprolactinemia. Other hormonal disorders include TSH (thyroid-stimulating hormone) deficiency in 45%, hyperprolactinemia in 37%, ACTH (adrenocorticotropic hormone) deficiency in 38.8%, and GH (growth hormone) deficiency in 20% [53]. Panhypopituitarism was noted in 25% of cases with pituitary dysfunction [43, 44]. Hyperprolactinemia is associated with 50% of cases with compression of the pituitary stalk [43, 44, 52]. According to other data, this correlation may be expected in even 78% of patients with hyperprolactinemia [53]. MR (magnetic resonance) imaging shows enlargement of the pituitary gland which is the most common finding and involves 80% of patients. A heterogeneous and homogeneous pattern of enhancement was described as often as an enlargement [52] although it should be emphasized that the imaging test may remain normal [43, 54]. Other imaging findings include pseudo-adenoma, loss of posterior hypersignal on T1-weighted images, and thickening or infiltrative lesions of the pituitary stalk [53]. The gland usually returns to its normal size after successful treatment [43, 55]. Granulomatous inflammation and inflammatory infiltrates are found in the pituitary gland tissue during biopsy [43, 53].

In a paper by Nishino et al., the prevalence of cerebrovascular events was 4% in patients with GPA [35]. Patients with GPA have an increased risk for stroke [56]. Central nervous vasculitis may be a cause of subarachnoid hemorrhage [57–59], intracerebral hemorrhage [60, 61], subdural hemorrhage [35, 62], arterial or venous thrombosis [63–65], and transient ischemic attack [66] or ischemic infarction of the cerebrum or spinal cord [43, 44]. Headaches, meningeal signs, encephalopathy, psychiatric syndromes, dementia, seizures, and strokes are symptoms which may suggest central nervous system involvement [67, 68]. The subclinical neuropsychological impairment can affect up to even 30% of patients with small vessel vasculitis [69]. Concomitant arterial hypertension, renal insufficiency, and iatrogenic impact of immunosuppressive therapy may be responsible for the symptoms mentioned above as well [67]. Cerebral vasculitis appears on MRI as white matter nonspecific lesions with high signal intensity made by the means of intermediate-weighted and T2-weighted images. Granulomas may be found on MR images as well [38]. Conventional angiography is not recommended for detecting small vessel vasculitis. Biopsy has huge limits because taking a sample is not often possible [44].

Cardiac Involvement

Cardiac involvement affects 3.3–44% of patients with GPA [3, 37, 70–72]. A review of the literature provides the information that pericarditis and coronary arteritis are the most common manifestations, both with the prevalence of 50% [73]. However, a study done by Morelli et al. shows that all patients examined by means of two-dimensional Doppler and color transthoracic Doppler echocardiography have cardiac abnormalities [74]. In another paper, 42% of patients with cardiac abnormalities attributed to GPA did not complain of any cardiac symptoms [75]. CMR (cardiovascular magnetic resonance) imaging is recommended to assess cardiac involvement in GPA [76, 77].

Heart involvement is frequent in patients with life- or organ-threatening forms of GPA, who did not achieve remission despite over 6 months of induction therapy [76]. Survival rates at 1 year and 5 years are 71% and 57%, respectively [75].

The frequency of pericarditis may concern even 6% of patients with GPA [3, 72] and may occur secondary to myocardial infarction or uremia in the course of kidney involvement [78–81]. Besides chronic constriction [71, 80], acute tamponade requiring an intervention occurs as well [78, 80, 82]. Coronary arteritis and subsequent thromboembolism may result in myocardial infarction [83] and leads to death [84]. The frequency of myocardial infarction is evaluated at 11% between patients with cardiac manifestations [73] and the coronary artery disease concerns 2.12% of GPA cases [72]. The inflammation can spread from arterioles to coronary arteries [85]. The occlusion of small-sized and medium-sized arteries may result in myocardial ischemia. Cocco et al. reported that angina and changes in ECG (electrocardiogram) disappeared after treatment with steroids and cyclophosphamide [86]. The myocardial involvement involves granulomatous foci, perivascular inflammation, and necrotizing vasculitis [73]. Myocarditis occurs in 25% of GPA cases with cardiac manifestations [73] and may lead to cardiomyopathy. The likely cause of cardiomyopathy may be cyclophosphamide therapy [37], but the main reason is granulomatous inflammation of the myocardium [81]. Endocarditis and valvulitis occur with a prevalence of 21% and are characterized histologically by inflammation, fibrinoid necrosis, and granulomatous masses [73]. Clinically significant endocarditis is very rare but it has been found during autopsy [81]. GPA can mimic clinically infective endocarditis [78, 87]. Valvulitis may occur as primary involvement of valves or secondary to dilation of the aortic root [71] or left ventricle [78] and appears as either stenosis or regurgitation [88]. Vegetations on valves are seen as well [86, 89]. In a study by Morelli et al., first, the aortic valve was affected and thickening and prolapse of valve was observed [74]. Epicarditis is noted in 8% of patients with heart involvement and shows granulomatous inflammatory foci [73]. The involvement of the conduction system results in arrhythmias [90]. The possible causes of such arrhythmias are granulomas of the conduction system or arteritis of the atrioventricular nodal artery. The most common arrhythmias are atrial tachycardia or atrial fibrillation or flutter [78] which may be a consequence sinus node location. This structure is located near the epicardium, so pericarditis may affect adjacent elements. Periatrial position may have an impact as well. Conduction

system granulomata were found in 17%, sinus node arteritis in 13%, and AV (atrioventricular) node arteritis in 13% of patients with cardiac involvement [73]. All types of cardiac block can occur including complete cardiac block [77, 78].

Some authors suggest that echocardiographic screening among patients with GPA may be a clinically valuable procedure because of the frequently silent course of cardiac involvement which correlates with increased morbidity [75, 91].

The definition of GPA includes necrotizing vasculitis concerning small-sized and medium-sized vessels but there are also known cases involving large vessels. The abdominal aorta is the most frequently affected vessel with a prevalence of 50%. Abnormalities of the thoracic aorta, the subclavian artery, and the internal carotid artery are observed as well. Changes include luminal stenosis, occlusion, wall thickening, periaortitis, and aneurysms. Periaortitis occurred with the highest prevalence (46%) [92]. An interesting case of a patient with retroperitoneal fibrosis and periaortitis was described [93]. Changes in large vessels respond well to rituximab in a case report described by Ozaki et al. [92].

Skin Involvement

There are no pathognomonic cutaneous manifestations for GPA [94]. Abnormalities of the skin occur in 14–50% of patients with GPA [3, 37, 79, 94–97] but some of these manifestations may be nonspecific or related to uremia [94]. Hu et al. showed that the amount of specific skin lesions was 28% [98] while Comfere et al. yielded results of 15% [97]. There are many possible presentations like palpable purpura, oral ulcers, skin nodules, skin ulcers, necrotic papules, gingival hyperplasia, pustules, palpebral xanthoma, genital ulcers, digital necrosis, livedo reticularis [95], petechiae, bullae, maculae, and erythema [94]. According to the results of some studies, palpable purpura is the most common manifestation [94–97] with even 35% of prevalence among patients with GPA and 74% of prevalence among dermatological findings [95]. A greater tendency to locate on lower limbs was observed [94] but lesions may also lie on upper limbs, head, neck [99], trunk [96], and parts of the genital organs [95]. The titer of c-ANCA was positive in 81% of cases with cutaneous manifestation. A prevalence of 79% referred to IgM (immunoglobulin M) immune deposits in leukocytoclastic vasculitis. C3 (complement component 3) deposits were observed as well but with lower occurrence [94].

A very interesting and rare cutaneous manifestation is pyoderma gangrenosum which occurs more frequently on the lower extremities as well which is the typical' localization. Obviously, other parts of the body may be affected (atypical form'). This entity is characterized by skin necrosis and development of deep ulcers. Pyoderma gangrenosum secondary to GPA is treated with standard immunosuppressive therapy. Kędzierska et al. presented a treatment-resistant case which was treated with dapsone and steroids and with the use of a hyperbaric chamber. The hyperbaric oxygen therapy resulted in the complete healing of wounds [100].

The histological findings include leukocytoclastic vasculitis, granulomatous inflammation, nonspecific ulceration, superficial dermal and epidermal necrosis without inflammation, erythema nodosum, granuloma annulare, chronic inflammation and acute inflammatory lesions without vasculitis. Leukocytoclastic vasculitis and granulomatous inflammation are the most common finding at biopsy both with a frequency of 31% [101]. But in another paper, the prevalence of leukocytoclastic vasculitis was much higher and equaled 80% [94].

Patients with lesions characterized by histologic features of leukocytoclastic vasculitis, palisading granuloma, granuloma vasculitis, abscess with granulomatous inflammation and necrotizing ulceration similar to pyoderma gangrenosum have higher prevalences of renal, ocular and central nervous system involvement. Furthermore, patients with cutaneous lesions are in a group with 80% risk for kidney involvement [94]. According to data from other studies, the prevalence of articular and renal involvement is higher among patients with skin changes [95] and with leukocytoclastic vasculitis. Interestingly, leukocytoclastic vasculitis is correlated with an earlier age range of GPA development and occurs approximately 15 months after the onset of GPA (35 months among patients with nonspecific chronic inflammation). The development of leukocytoclastic vasculitis compared with no skin lesions is connected with a more rapidly developing and widespread GPA [101]. The appearance of skin abnormalities may announce active systemic disease. Such appearance responded well to standard treatment in one study [95].

Gastrointestinal Tract Involvement

Some changes in the gastrointestinal tract may be caused by glucocorticosteroid therapy [102, 103]. However, there are known cases without the use of immunosuppressant drugs [104, 105]. The literature shows an approximate 10–26% prevalence of gastrointestinal tract involvement [39, 104–106]. However, in a study done by Hoffman et al., there were no cases showing evidence of change in the gastrointestinal tract [3].

Patients complain of abdominal pain, gastrointestinal bleeding, dyspepsia, vomiting, and diarrhea [105]. Abdominal pain is the most common of these symptoms and affects almost all patients (97%). Other clinical presentations occur with lower prevalence: nausea or vomiting–34%, diarrhea–27%, hematochezia or melena–16%, and hematemesis–6% [107]. Differential diagnosis needs to distinguish gastrointestinal involvement secondary to GPA from coeliac

disease, ulcerative colitis, Crohn's disease, ulceration, perforation, hemorrhage [108], and other vasculitis like Churg-Strauss syndrome and polyarteritis nodosa [102]. Some lesions due to vasculitis need surgical intervention [107].

CT (computed tomography) findings include multifocal or diffuse wall thickening, abnormal bowel wall enhancement, mesenteric vascular engorgement, and ascites [109], whereas, endoscopic examination reveals ulcerations with the majority being located in the upper gastrointestinal tract (esophageal ulcerations–7% and gastroduodenal ulcers–17%). Colorectal ulcerations occur in 6% of endoscopies [107]. The development of ulcers is probably caused by blood supply impairment due to vasculitis [102]. Walton et al. did not find any granuloma in the intestine but features of focal necrotizing vasculitis was noted in 24% of cases during autopsy [39] whereas, Storesund et al. proved vasculitis in 3 of 7 patients in the study. In the remaining cases, biopsy showed ulceration, ischemic changes, or inflammation [110]. But the histopathological diagnostic difficulties may result from immunosuppressive therapy administration [111].

Joints and Muscles Involvement

Articular or muscular abnormalities concern 4.7–67% [3, 37, 112] with the main complaint being arthralgia (generally polyarthalgia [37]) of the knees, hips, wrists, or ankles [112]. The diagnosis of arthritis is established in 28% of patients. Hoffman et al. and Fauci et al. noted that articular deformities did not occur in their studies [3, 37]. Jacobs et al. presented a patient with GPA who had erosive arthritis. Lesions responded well to cyclophosphamide [113].

Articular manifestations are usually associated with disease activity [113]. The symmetrical involvement of joints and the false-positive results of rheumatoid factor lead to incorrect diagnosis of rheumatoid arthritis [3]. But there are known cases of granulomatosis overlapping with polyangiitis and rheumatoid arthritis [114]. According to the results of one paper, even one half of patients with GPA can have a positive rheumatoid factor [115].

Despite remission, a patient may still suffer from arthralgia. Fortunately, patients responded well to nonsteroidal anti-inflammatory drugs in one study [37].

Muscular involvement includes myalgia, weakness, and muscle enzyme elevation [116].

Besides arthralgia, arthritis, or myalgia, there are interesting findings like soft tissue calcifications, sacroiliitis, relapsing polychondritis [115], or GPA-mimicking psoas abscess [117].

Ophthalmological Involvement

The prevalence of ocular changes occurs in 30–58% of cases [3, 37, 39, 79, 118]. GPA may involve the orbit, sclera, episclera, cornea, conjunctiva, eyelids, nasolacrimal system, optic nerve, retina, and uvea [119].

Orbital involvement occurs in 45% of cases of ocular and adnexal involvement and is characterized by orbital pain, proptosis, limited movements of extraocular muscles, erythematous edema of the eyelids [119], diplopia, and deterioration of vision [120]. The most common manifestation was proptosis [3, 121] and was refractory to treatment in a Fauci et al. study [37]. The likely mechanism of these abnormalities may be a direct result of inflammation or be caused by a spreading process from contiguous tissues [122, 123]. Retro-orbital tumor mimicry was described earlier in this paper.

Eyelid abnormalities (20% [119]) include edema, entropion, trichiasis and xanthelasma [120], and ptosis. It has been noted that eyelid involvement is most frequently associated with orbital involvement [119].

Nasolacrimal manifestations may be expected in 25% of patients with ocular and adnexal involvement [119]. The changes in the orbit may spread from dacryoadenitis [124]. The inflammation may appear recurrently. Patients complain of epiphora due to the obstruction of this gland [119]. The features of acute and chronic inflammation and focal vasculitis of small vessels are found in biopsy [125].

Inflammation of small vessels in the conjunctiva may result in conjunctivitis [126] (15% [119]) which may lead to plaque-like lesions, ulcerating lesions [127] or avascular, necrotic tissue [128]. The involvement of conjunctiva may end in its cicatrisation [129]. Mucopurulent discharge is observed as well [119]. One study describes the prevalence of tarsal conjunctivitis among 16% of patients with GPA [128].

The involvement of episclera and sclera occurs with a frequency of 38% among patients with ophthalmic manifestations [119]. Scleritis can appear diffuse, nodular, necrotizing, softened (scleromalacia) and posterior, whereas episcleritis can appear simple and nodular [130]. The diffuse form is the most common among patients with ANCA-positive vasculitis [131]. Ocular complications connected to episcleritis and scleritis are decreased vision, anterior uveitis, peripheral ulcerative keratitis, glaucoma, and cataract [132]. There is a report of a patient who needed an enucleation due to severe pain and necrotizing scleritis [119].

Twenty-eight percent of patients with ocular and adnexal involvement have changes in the cornea. Photophobia, pain, marginal subepithelial infiltrates, pannus, thinning, and ulcerations may be possible signs and symptoms [119]. The involvement of the peripheral cornea is caused by vasculitis of intrascleral portions of the anterior ciliary arteries, perilimbal arteries, or both. Peripheral ulcerative keratitis is often bilateral [133] and is connected with 14% of cases with scleritis [132]. Descemetocele and central corneal ulcers were described as well [119, 134].

Uveal manifestations comprise 10% of ocular and adnexal involvement [119]. Anterior, intermediate, and posterior parts

may be affected. Vitritis may coexist with these uveal manifestations [120]. Anterior uveitis is associated with scleritis [132] and is the most common form of uveitis (70%) among patients with ANCA-positive vasculitis [131].

Retinal involvement concerns 18% of patients with ocular and adnexal involvement [119]. Fauci et al. noted retinal artery occlusion in their study [37]; however, retinal abnormalities found also include edema of the optic disk with retrobulbar mass, retinal hemorrhages and edema [119], chorioretinitis, macular edema, retinitis with cotton wool spots, acute retinal necrosis, peripheral retinitis, exudative retinal detachment, and central retinal vein occlusion. The mechanism occurring in retinal vein occlusion is probably similar to that which is responsible for renal involvement [135]. Occlusion of retinal vessels may lead to choroidal infarct [136, 137]. Histopathological examination shows lymphocytic infiltration throughout the choroid and marked sclerosis of choroidal vessels with thickening of the media and prominent endothelial cells [137].

The involvement of the optic nerve occurs with a prevalence of 22% among patients with ocular presentations [119]. Vasculitis, acute compression, or stretching with to the point of vascular compromise may affect the optic nerve [126]. It should be kept in mind that approximately 50% of patients with retro-orbital tumor lost their vision as a result of optic nerve ischemia [3]. Anterior ischemic optic neuropathy [138] and posterior ischemic optic neuropathy [139] were observed. Eight percent of patients with eye disease lost vision in a Hoffman et al. study [3].

Conclusions

GPA is a huge challenge for contemporary diagnostics and medicine. We emphasize that every doctor should be aware of GPA's existence despite its rare prevalence. Particularly, the viability of a GPA diagnosis should be considered when a patient's condition does not improve despite a presumably proper therapeutic regimen. Our review provided the multiplicity of untypical manifestations and proved that every specialist may come into contact with a patient with GPA.

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Compliance with Ethical Standards

Ethics Approval and Consent to Participate Not applicable.

Ethical Statement This article is a review. An approval of Bioethics Committee is not required.

Competing Interests The authors declare that they have no competing interests.

Abbreviations GPA, granulomatosis with polyangiitis; ANCA, antineutrophil cytoplasmic antibodies; PR3-cANCA/ c-ANCA, proteinase 3 antineutrophil cytoplasmatic antibodies; MPO, myeloperoxidase; MRI, magnetic resonance imaging; MR, magnetic resonance; TSH, thyroid-stimulating hormone; ACTH, adrenocorticotropic hormone; GH, growth hormone; CMR, cardiovascular magnetic resonance; ECG, electrocardiogram; AV, atrioventricular; IgM, immunoglobulin M; C3, complement component 3; CT, computed tomography

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