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REVIEW

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Atypical manifestations of granulomatosis with polyangiitis: the diagnostic challenge for pulmonologists

Abstract

This is a review considering atypical manifestations of granulomatosis with polyangiitis (GPA). Virtually any organ can be affected, and in some patients, GPA can manifest unusually. Since thoracic involvement of GPA often predominates, the first who might be expected to establish a diagnosis are pulmonary specialists. We would like to familiarize pulmonary specialists with several extra-ELK (E: ear-nose-throat; L: lung; K: kidney) involvements of the disease. We describe sites rarely affected by GPA like the breast, skeletal system, orbit and eye, heart and vessels, central nervous system, urogenital system as well as endocrine and gastrointestinal tract involvement.

Key words: granulomatosis with polyangiitis, atypical manifestations, diagnosis, therapy, vasculitis

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Introduction

Granulomatosis with polyangiitis (GPA) is an uncommon necrotizing inflammation of small arteries and veins (*vasculitis*). It classically involves the vessels of the lungs, nasal passages, ear, throat and kidneys, and clinically manifests as a triad consisting of upper and lower airway disorders and glomerulonephritis. GPA can affect people at any age, although it is uncommon in children. Usually, GPA affects young or middle-aged adults. The cause of GPA remains unknown. However, the association of small vessel vasculitis with antineutrophil cytoplasmic antibodies, which are usually specific for proteinase 3, has yielded a new insight into pathogenic mechanisms [1]. Treatment depends on the extent of involvement and clinical course. In modern treatment strategies, intensive immunosuppressive therapy with a high dose of corticosteroids and cyclophosphamide or rituximab are used to induce remission [2, 3]. Once remission is achieved, patients are switched to less toxic maintenance immunosuppression, such as azathioprine and a low dose of corticosteroids. Normally, GPA responds quickly to immunosuppressive therapy, and prognosis, mainly limited by renal and pulmonary involvement, is rather good without higher mortality.

The wide range of clinical presentations is encompassed by ELK (E: ear-nose-throat; L: lung; K: kidney) classification, in which any combination or singular involvement of the major sites can be considered within the disease spectrum if supported by the appropriate pathologic or laboratory findings (the presence of a cytoplasmic antineutrophil cytoplasmic antibodies; cANCA). Other less frequently involved organ systems include the central and peripheral nervous system, skin, muscles, large joints, heart and eyes. Rarely, numerous other sites can be affected. Virtually any organ can be attacked, and in some patients, GPA can manifest unusually. Since thoracic involvement of GPA often predominates, the first who might be expected to establish a diagnosis are pulmonary specialists. Therefore, they should be aware of those less frequent mani-

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festations, seemingly not compatible with GPA or even mimicking other diseases, and keep in mind that limited forms of GPA with oligosymptomatic and atypical site involvement might occur. Thus, this awareness may be also useful when any new atypical manifestations occur in the course of disease with established diagnosis of GPA. Therefore, we would like to familiarize pulmonary specialists with several extra-ELK involvements of the disease.

Breast

Two reviews of the literature showed that breast involvement has been rarely reported in the literature [4, 5]. The most extensive review of the entity has been presented by Allende and Booth [4] and included 27 cases reported both in English and other languages. In turn, in their systematic review, Ren *et al*. [5] excluded reports published in non-English languages and not published in peer-review journals, and found 23 relevant cases. In Poland, two cases of breast involvement in GPA with lung and renal manifestations were described until now [6, 7]. The majority of cases regarded women between the third and seventh life decade and accompanied by systemic manifestations of the disease [4]. The GPA of the breast was usually unilateral and concomitant with lung and other organs involvement [8–13], although breast lesions can occur as the initial symptom of the disease [8, 12]. These lesions presented usually as nodules or masses, sometimes poorly circumscribed and of a firm consistency, with or without extensive necrosis (Figure 1). Such an appearance of the lesions resembled neoplastic disease of the breast [4, 14–15]. Occasionally, an association of a tumor-like lesion of the breast with multiple lung nodules strongly suggested a presumed diagnosis of metastatic carcinoma [12]. In any case, excluding breast carcinoma from the clinical differential diagnosis is required.

Skeletal system

Bones are involved in the course of GPA very rarely, except for facial bone involvement (mainly nasal septum destruction and sclerosing osteitis) associated with destructive inflammation of nasal passages and sinuses, or temporal bone (most often manifested as a mastoiditis). Clinical appearance of other bones involvement with GPA, concomitantly with lung involvement, has been described in single case reports. These include a case report presenting a 54-year-old man with

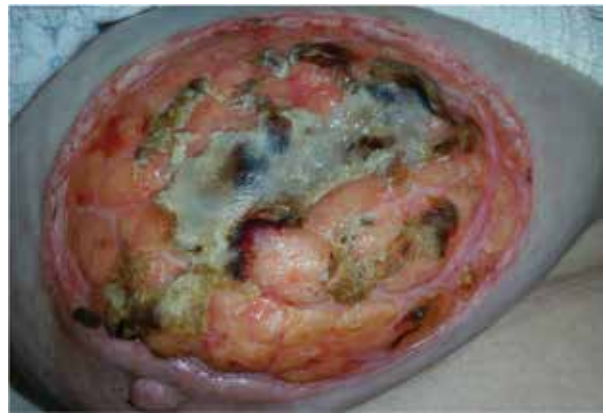

Figure 1. Well-with demarcated large ulceration central necrosis of right breast in the course of GPA

mass-like lung lesions accompanied by sternal osteomyelitis and destructive arthritis around the sternoclavicular joint [16]. Initial treatment with antibiotics and immunosuppressive therapy was non-effective and a new lung lesion occurred. A histopathological investigation of the lung mass showed chronic granulomatous inflammation with fibrinoid necrosis, findings accordant with GPA. In other case, granulomatosis with polyangiitis affected the scull base and manifested as a spontaneous skull base osteomyelitis with the development of cranial nerve palsies [17].

Another rare limited form of c-ANCA-positive GPA started with the bluish discoloration of the fingertips of both hands leading to spontaneous resorption of digits with acro-osteolysis [18]. The lesions were accompanied by general symptoms, including intermittent fever, myalgia and weight loss with an almost asymptomatic solitary cavitating nodule of the lung detected on high-resolution chest computed tomography. Sequentially, the patient displayed mononeuritis multiplex symptoms.

Although facial bone destruction as the most frequent bone manifestation of GPA mainly affects the nasal septum, contiguous granulomatous infiltration may spread to the soft tissues of the orbit and/or eye [19].

Orbito-ocular involvement

The orbit and eye are two of the most frequent body sites that could be affected by both granulomatous inflammation and focal ischemic vasculitis in the course of GPA. Ophthalmic involvement has been reported in up to 60% of patients diagnosed with GPA [20]. Orbital inflammation and necrotizing keratoscleritis,

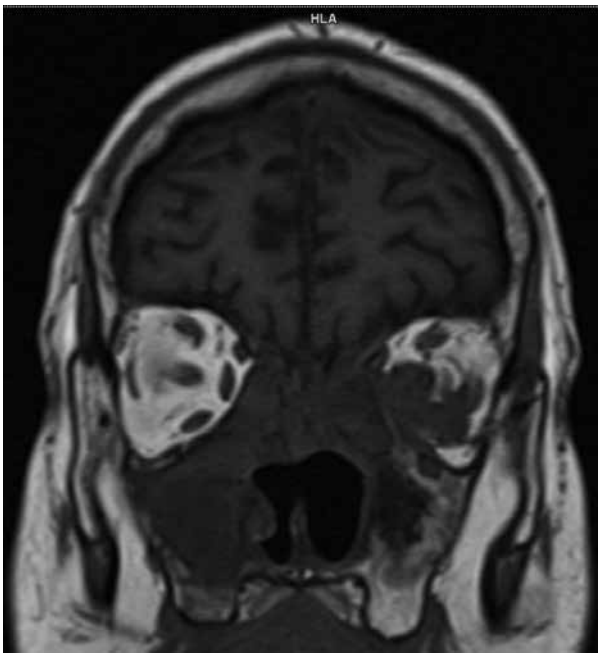

Figure 2. Orbit MRI, T1-weighted coronal image showing contiguous infiltration which spreads from the ethmoid sinus to the left orbit. Some of the oculomotor muscles and optic nerve are infiltrated

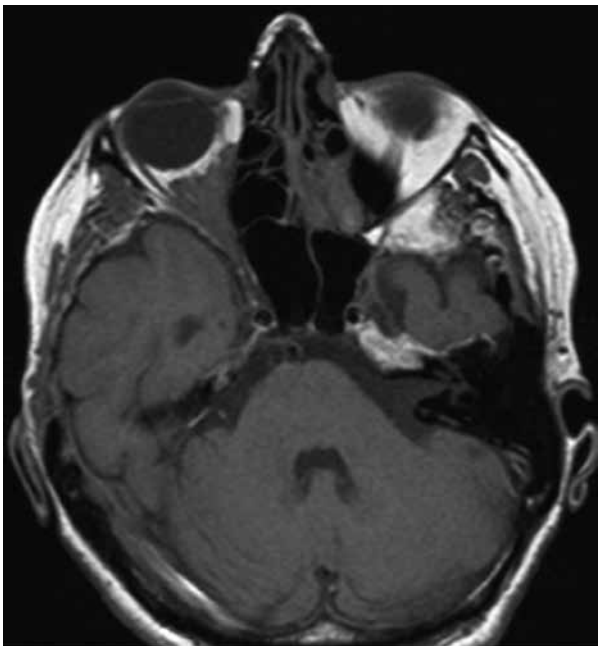

Figure 3. Orbit MRI, T1-weighted axial image showing infiltration of the right orbit which includes oculomotor muscles

episcleritis or conjunctivitis are the most characteristic presentations. Uveitis and granulomatous vasculitis of the retina and optic nerve are also relatively common ophthalmic manifestations of GPA. In turn, orbital mass is a rare presentation in GPA patients. In the study comprising 1,142 patients with GPA, only 5% developed orbital masses during a 5-year follow-up [21]. However, it is noteworthy that profound examination initiated by the presence of orbital mass may reveal asymptomatic pulmonary lesions [22]. Usually, orbito-ocular manifestations represent limited form of GPA but can be also the first presenting feature of GPA before progression to the lung and/or multisystem involvement [20, 23]. Thus, pulmonologists may encounter cases with pulmonary-renal involvement associated with initial orbito-ocular symptoms [24]. The presence of unexplained orbital inflammatory disease (Figures 2 and 3) in patient with pulmonary abnormalities in radiological imaging, should raise the question of possible GPA. A thorough clinical examination, laboratory testing and histological examination of lung biopsy specimens are essential to diagnose GPA and exclude potential mimics [25]. In turn, conjunctival ulceration as the presentation of GPA is rarely reported, and its occurrence in patient with remission of the disease may alert renewed systemic disease activity [26]. Few case reports have also claimed attention to rare orbito-ocular manifestation of GPA — acute unilateral dacryoadenitis, which may precede upper and lower respiratory tract involvement [27–29].

Ophthalmic lesions in the course of GPA can result not only from the involvement of soft tissues of the orbit but also from the involvement of the central nervous system, namely meningeal. For instance, because of morphological similarity and the anatomical continuity between the meningeal and the perioptic tissues, granulomatous inflammation may spread along such tissue planes and even lead to visual loss [24]. In other rare cases, optic neuritis in GPA without signs of orbital involvement is most likely caused by occlusive vasculitis of the vasa nervorum [30]. In every case, ocular lesions should be recognized as soon as possible so that an early diagnosis may allow appropriate treatment and good visual and general prognosis.

Nervous system involvement

The involvement of the nervous system by GPA, mainly as a peripheral or cranial mononeuritis multiplex, occurs relatively frequently, affecting 22–53% of patients [31–32]. Involvement limited only to the central nervous system (CNS) has been reported less frequently, in 2–8% of cases [32–33]. However, the use of new diagnostic

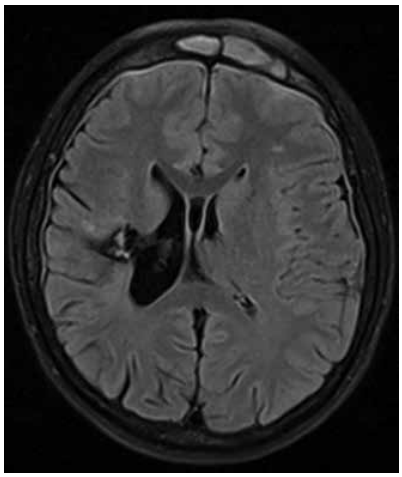

Figure 4. Brain MRI, FLAIR axial image showing chronic ischaemic stroke of the right hemisphere with retraction of the lateral ventricle. The thickening of meninges and frontal sinus inflammation are also seen

procedures, including modern neuroimaging, allowed detection of CNS involvement in up to 13% of GPA patients [34].

Three different types of nervous system involvement have been enumerated: 1) necrotizing vasculitis affecting the cerebral, spinal, and radicular vasculature; 2) direct granulomatous infiltration from contiguous lesions in the nose, paranasal sinuses and orbits; and 3) primary necrotizing granulomas in the skull, meninges, brain or cranial nerves [35].

The first type is the most common, and both peripheral and cranial neuropathies are thought to be caused by the small vessels vasculitis [35]. Case reports on cranial neuropathies in GPA prove the true diagnostics difficulties, because sometimes the diagnosis is possible only when lung and/or renal extension of GPA follows its initial neurological manifestation [36–38]. Larger brain arteries are involved extremely rarely [39]. The unique case of GPA with paranasal sinuses, pulmonary and renal manifestations, and concomitant intracranial aneurysm of the anterior choroidal artery, complicated by rupture and subarachnoid hemorrhage, has been reported by Takei *et al*. [39]. Necrotizing vasculitis was also a pathogenic mechanism of ischemic infarction in few case reports [40–41].

Contiguous invasion of granuloma in CNS from extracranial sites of GPA, such as nose, paranasal sinuses and orbits has been incidentally described (Figures 4, 5A, 5B) [42]. Most often the pathogenic mechanism of lesions found in CNS is isolated cerebral or meningeal granulomatous inflammation.

Cerebral meningitis is one of the most frequent manifestations following cerebral ischemic or hemorrhagic lesions, observed in 42% of patients

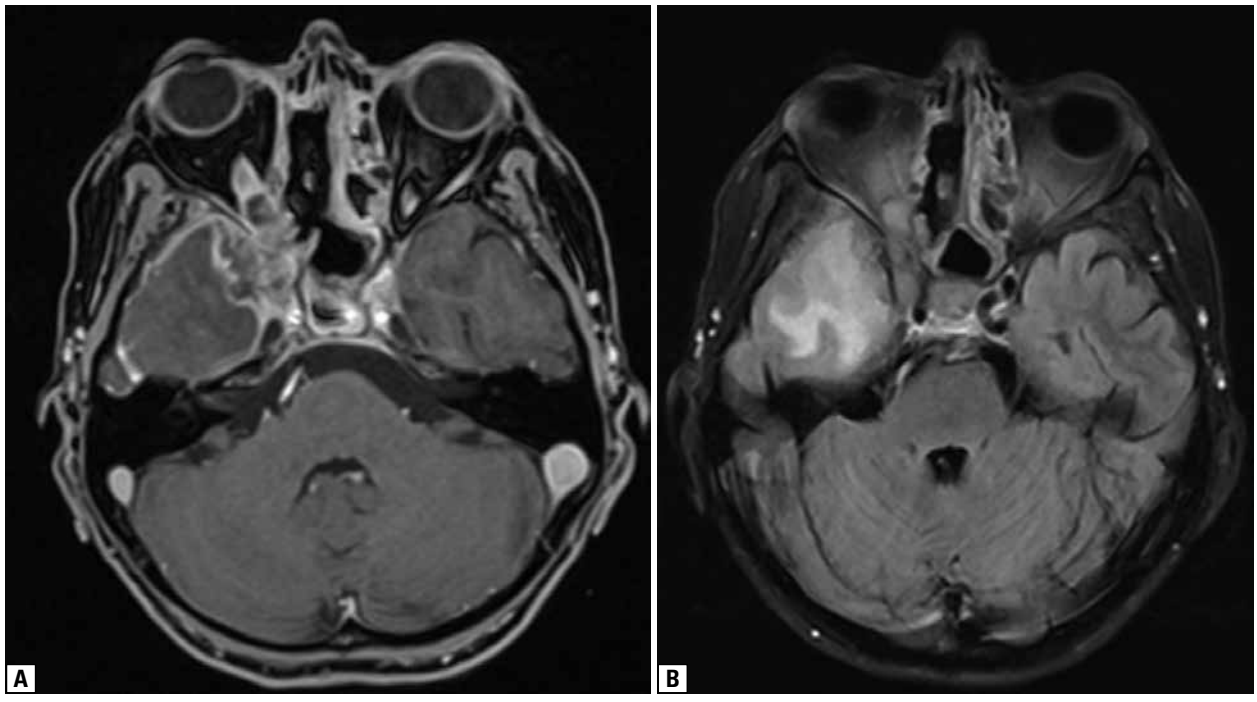

Figure 5. Brain MRI. **A.** T1-weighted axial image with contrast enhancement. Images showing contiguous, contrast enhanced infiltration spreads from the posterior ethmoid sinus to the cavernous sinus, dura mater and the temporal lobe; **B**. FLAIR axial image. Local brain edema around imflammatory changes is also seen on FLAIR image

with GPA and CNS involvement [43]. That manifestation is considered to represent granulomatous infiltration of the dura mater of the brain and because the leptomeninges (pia and arachnoid) are affected incidentally, the terms pachymeningitis, hypertrophic pachymeningitis, or chronic hypertrophic pachymeningitis are commonly used referring to this condition. Moreover, whereas such neurological manifestations of GPA as mononeuritis multiplex, peripheral neuropathies, ischemic stroke, or intracerebral or subarachnoid hemorrhage are quickly put to diagnostic process, headache, a common symptom in meningeal involvement is often considered a symptom of chronic sinusitis or orbital disease. Pachymeningitis in the course of GPA may remain unrecognized for a long time [44], which in turn, can lead to delay in accurate diagnosis and timely treatment preventing serious local damage of the CNS. Pulmonologists should keep in mind that although pachymeningitis is associated with localized form of GPA, in single cases it was reported also in patients with lung involvement [45–48]. Therefore, in GPA patients with recent onset of severe headache, pachymeningitis should be considered and cranial MRI performed. This diagnostic procedure may reveal general thickening and pronounced enhancement of all meningeal structures.

Spinal dural and cord involvement presents as a spinal dural mass and in comparison to pachymeningitis, it is reported less frequently, and relapses are more often observed [43, 49]. It can be the initial GPA manifestation [50] or it can accompany other organs involvement, including the lungs, which pulmonary specialist should be aware of [49].

Cardiac involvement

Cardiac involvement in GPA is rare and usually associated with a threat of serious cardiac events and clinical courses refractory to immunosuppressive therapy. In the large multicenter North American study comprising 517 patients with GPA, cardiac involvement was shown in 3.3% [51]. Generally, all cardiac structures can be affected, but the most common cardiac manifestation in that study was pericarditis (35%) followed by cardiomyopathy (30%) and coronary artery disease (12%). Less frequent manifestations included valvular disease (6%) and severe conduction disorder (6%) [51]. However, the usage of magnetic resonance imaging in the study performed by the French Vasculitis Study Group revealed that specific cardiac involvement in GPA may be underestimated [52]. For instance, pericarditis was detected in 26% of all studied GPA patients and late gadolinium enhancement, mostly nodular, in 32% of subjects. The reason for underdiagnosing cardiac manifestations of GPA is probably the fact that many of them can be subclinical or clinically asymptomatic [53–54]. Therefore, cardiac involvement in GPA was stated in only few case reports of congestive cardiomyopathy [55–57], myocarditis [58–61] and other cardiac conditions related to GPA [57, 62–65]. In case of coronary arteries involvement, it is noteworthy that clinically acute coronary syndrome in a patient with lung involvement can develop with no significant stenosis at catheterization [64]. Rhythm problems as a clinical cardiac manifestation of GPA with lung involvement are infrequent. The most often reported rhythm problems are supraventricular arrhythmias, followed by varying degree of heart block [57, 62–63]. Cardiac valvular involvement has been also rarely reported but it is a potentially fatal complication of GPA. In addition, this cardiac manifestation may misleadingly suggest infectious endocarditis [65]. To summarize, pulmonary specialists should remember that cardiac involvement in a GPA patient is heterogenous and can be usually clinically nonapparent, although potentially life- threatening [63]. They should also take into account that stenocardia symptoms or any other cardiac symptoms in a patient with suspected or confirmed GPA can indicate cardiac involvement. Profuse diagnostics, including magnetic resonance imaging, should be performed because confirmation of cardiac involvement dictates more aggressive treatment.

Systemic and regular cardiac assessment in the follow-up of patients with GPA is also recommended.

Large vessel vasculitis with or without aneurysm formation

Vasculitis of the large vessel with or without aneurysmatic changes is not typical finding in GPA. However, a review of the literature revealed a number of cases in which the involved arteries included the aorta [66–74], gastric [75], subclavian [76], pulmonary [74] and internal carotid artery [39]. In most instances, depending on the artery affected, abdominal pain was the presenting symptom [66, 68, 70–71]. In other cases, back pain [69, 72], arm pain [76], headache due to subarachnoid hemorrhage [39] and atrioventricular block were the presenting symptoms. In most of the cases, involvement of large vessels was

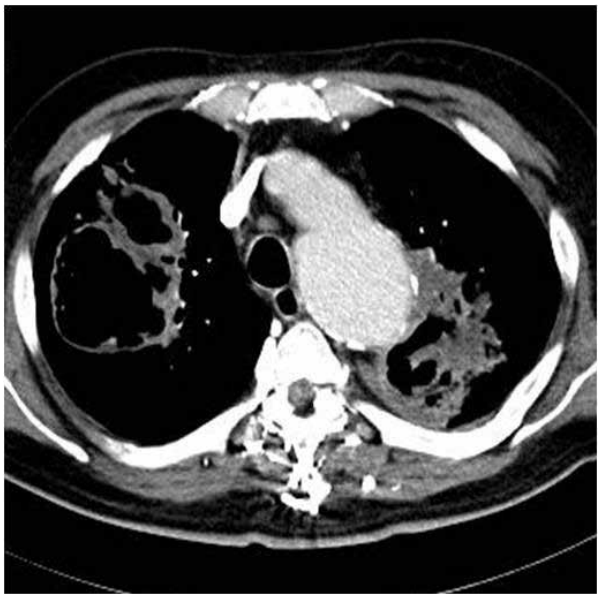

Figure 6. Axial chest CT scan. Large saccular aneurysm of aortic arch and descending aorta adjacent to pulmonary cavitary lesion

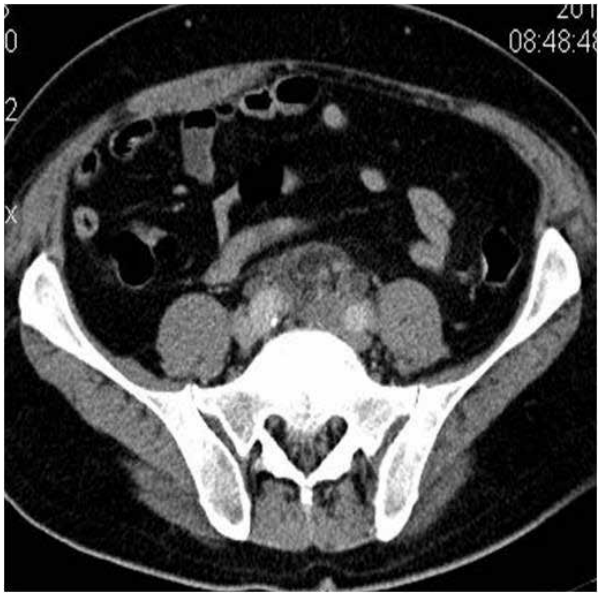

Figure 7. Abdominal CT scan. Retroperitoneal inflammatory infiltration involving iliac vessels and left urether causing hydronephrosis in 48 years old man with GPA

shown simultaneously at the time of diagnosis of GPA with pulmonary involvement (Figure 6) [39, 68–69, 71–74, 76], but clinical presentation of large vessels can manifest several months before [66] or after the diagnosis [70].

It seems justifiable to consider GPA in differential diagnosis of unexplained abdominal pain when aortic aneurysm is found [68, 71]. Especially, when a young patient presents with abdominal aortic aneurysm, GPA may be an underlying cause [71]. The early diagnosis is of great importance, because surgical treatment (vascular intervention) and immunosuppressive agents prevent a development of further aneurysm, which is a life-threatening complication.

Urogenital manifestations of GPA

Urogenital manifestations of GPA are found relatively rarely — in less than 1% of patients [77–80]. They can be present at the onset of the disease, together with lower respiratory system manifestations, sometimes as its first clinical evidence (Figure 7). In other cases, they appear before subsequent development of pulmonary involvement of GPA or as a symptom of GPA relapse [79, 81]. Symptomatic urogenital manifestations in case reports with concomitant lung involvement included prostatitis [79, 82], epididymitis [79, 81], renal mass [79], ureteral stenosis [82], and penile ulceration [83–84]. Some presentations, such as a renal or prostate mass, mimic cancer or an abscess. Considering GPA in the differential diagnosis might help avoiding unnecessary radical surgery, especially that urogenital symptoms can be promptly resolved with corticosteroids and/or immunosuppressive agents.

Endocrine involvement

Endocrine involvement, particularly of the thyroid gland, adrenal gland and hypopituitary is extremely rare. The single case reports describing cold thyroid nodules or suprarenal mass of GPA origin and concomitant pulmonary GPA involvements have been published to date [85–87]. Regarding pituitary involvement in GPA, recent search for the cases indicated in the literature revealed 58 published reports. This rare complication more frequently affected females (69%) than males [88]. Moreover, pituitary involvement has predominantly concerned posterior gland and is usually associated with other organ involvement [88, 89]. Numerous patients (43–73%) with pituitary manifestation of GPA have concomitant lung lesions [88, 89]. Cranial diabetes insipidus was the most common endocrine abnormality found in 81% of cases [88]. Anterior pituitary hormone abnormalities, including hypogonadism, secondary hypothyroidism, hyperprolactinemia and growth hormone deficiency, are less frequent. Pulmonologists ought to keep in mind the possibility of pituitary involvement. In every patient with pulmonary presentation of GPA who displays unusual

symptoms such as polydipsia and polyuria, this rare involvement should be considered [90, 91].

Gastrointestinal tract involvement

GPA as a predominantly renopulmonary disorder rarely has gastrointestinal system manifestations and the involvement of this system usually occurs long after the onset of initial symptoms [92]. Among them, the pancreas, liver or colon involvement is exceedingly rarely reported [92–95]. For instance, only single case reports described overt clinical manifestation of pancreatic GPA, including painless jaundice or recurrent acute pancreatitis as an initial presentation of GPA or presentation concomitant with the typical pulmonary and/or renal involvement [93–94]. Moreover, when a patient with established GPA develops otherwise unexplained acute pancreatitis, reactivation of the disease should be considered by pulmonologists [93]. Thus, involvement of the pancreas, although uncommon, should be taken into account in the differential diagnosis in cases of abdominal pain with hyperamylasemia or cases clinically mimicking pancreatic carcinoma.

Similarly, liver involvement in GPA is very rare with only few case reports in the literature, presenting patients with concomitant systemic disease affecting the lungs [95]. Though very infrequent, this organ involvement is potentially fatal due to a risk of liver failure. Therefore, it should not be forgotten as a manifestation of GPA.

There are also few case reports of gastric and intestinal involvement where severe colitis with gastrointestinal hemorrhage was a presenting feature of GPA preceding further progression of the disease with pulmonary and other organs manifestations [92, 96–97]. Other single cases reported colitis following initial pulmonary and/or other organs manifestations of GPA [98–102].

Conclusions

The presented atypical organ involvement of GPA does not exhaust the topic of all possible manifestations of the disease. Any nonspecific illness concomitant with pulmonary lesions in GPA patients should raise the suspicion of unusual involvement of the disease, and differential diagnostics is required to confirm or exclude this suspicion. Understanding of a broad spectrum of possible organ involvement in GPA, sometimes potentially fatal, may help in timely diagnosis and treatment.

Therefore, collecting data in registry for GPA patients (e.g. POLVAS in Poland) and cooperation among registries, will broaden our knowledge about the disease and have impact on directions in future research. Proper diagnostics of patients with atypical GPA manifestations is very important, as it allows the implementation of appropriate treatment according to the current guidelines of the American College of Rheumatology (ACR), as well as British Society of Rheumatology and British Health Professionals in Rheumatology (BSR and BHPR).

Conflict of interest

None declared.

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