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Development of granulomatosis with polyangiitis in the patient with chronic myeloid leukemia: a case report and a short review of literature

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Abstract

The association of granulomatosis with polyangiitis (GPA), a form of antineutrophil cytoplasmic antibodies-associated vasculitis (AAV), with neoplastic disease was reported. Most of the described cases are malignancies that develop in patients after long-term vasculitis medication.

The purpose of this paper is to review a rare case of the development of GPA in a patient suffering for more than a decade from chronic myeloid leukemia (CML). Such an association was a challenge for differential diagnosis because it had been initially considered a transition to the accelerated phase of CML or the development of secondary malignancy. Finally, a diagnosis of GPA was established, and medication with cyclophosphamide and subsequently with rituximab was administered. Such management, together with the continuation of medication against CML, led to significant improvement.

The possible associations between vasculitis and malignancy and their clinical implications were discussed.

From the point of view of clinical practice, it is important to remember that a diagnosis of a malignant disorder does not exclude the occurrence or new development of an autoimmune disease. Moreover, the symptoms and signs of both maladies may be akin, and an in-depth differential diagnosis is needed.

Key words: granulomatosis with polyangiitis; antineutrophil cytoplasmic antibodies-associated vasculitis; chronic myeloid leukemia

Introduction

Granulomatosis with polyangiitis (GPA) is a rare disorder of unknown etiology, characterized by necrotizing granulomatous inflammation of the upper and lower respiratory system, kidneys, and several other organs [1]. GPA is classified as antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (AAV), and together with microscopic polyangiitis account for ~80–90% of all AAV [2, 3]. ANCA are autoantibodies directed against antigens found in the cytoplasmic granules of neutrophils and monocytes. They are believed to be involved in the development of AAV and are an important diagnostic tool in patients with those subgroups of systemic vasculitis [4].

The relationship between GPA and malignancy is commonly considered in two aspects. The first one is GPA as a risk factor for the development of various malignancies. It is well known that autoimmunity and associated inflammatory response facilitate the development of neoplastic disease [5–8]. Additionally, the application of cyclophosphamide or other immunosuppressants can cause an enhanced risk of malignancy.

There are a few studies focusing on the cancer risk in patients with AAV. All the published observations indicated 1.6–2.4 times higher cancer risk for AAV patients as compared to the general population. Heijl et al. [3] recently published observations of about 1500 person-years and found that the standardized incidence ratio (SIR) for cancers at all sites was 2.8. SIR for all cancers, excluding squamous cell carcinoma, was 1.8, SIR for squamous cell carcinoma was 12.9, SIR for bladder cancer was 4.3, and SIR for pancreatic cancer was 7.0. The last two cancers are believed to be an adverse reaction to cyclophosphamide treatment. The relationship between the cumulative dose of cyclophosphamide and

malignancy was revealed in most of the papers. In contrast to these papers, the study of Heijl et al. [3] does not show an association between cumulative doses of cyclophosphamide < 10 g and a higher incidence of cancers other than squamous cell carcinoma. All the studies considered AAV as a group, and there are very scarce data on the effect of GPA on malignancy.

On the other hand, GPA was a dominant form of AAV in investigated populations; thus, it can be concluded that GPA is a significant risk factor for malignancy similar to autoimmune disorders like dermatomyositis. Limited studies and case descriptions indicate that GPA, as well as long-term administration of cytotoxic agents, is associated with the development of hematological malignancies. The main hematologic malignancies complicated by GPA patients are myelodysplastic syndrome or acute myeloid leukemia [9]. A number of case reports indicate lymphoma as a neoplastic complication of GPA.

The second aspect of the relationship between GPA and malignancy is the difficulties in diagnosing GPA and various neoplastic diseases, especially in the upper respiratory system [10]. In most cases, histopathological evaluation of the tissue samples and the lack of malignant cells, but the occurrence of necrotic vasculitis, was crucial for the diagnosis.

The paper was designed to report an unusual situation regarding the development of GPA in patients with an established diagnosis of chronic myeloid leukemia (CML) and review the diagnostic difficulties in the case.

Case presentation

A 53-year-old Caucasian male suffering from CML was referred to our Department of Rheumatology and Internal Medicine in March 2022 after hospitalization at a few other wards. Diagnosis of CML was made in 2010. The patient had reported intermittent low-grade fever, weight loss, and weakness. Leukocytosis (34 G/L), thrombocythemia (417 G/L), and lack of features of active urine sediment had been revealed. He underwent a bone marrow biopsy, which was consistent with CML in the chronic phase (rich cell smear, granulocytic system constituted approx. 59.5%; myeloblasts 0.5%, promyelocytes 2.5%, myelocytes 16.6%, metamyelocytes 10.5%). The Philadelphia chromosome had been found, and the presence of the *BCR/ABL1* fusion gene had been confirmed in 81% of the analyzed cells. Hepatosplenomegaly was detected ultrasonographically, and no abnormalities were shown in

computed tomography of the chest and abdominal cavity. The patient was started on imatinib at a daily dose of 400 mg. In January 2022, the patient was noted to have worsening exercise tolerance, weight loss (approx. 10 kg in 3 months), and purpura-like skin changes on the lower limbs. Cutaneous symptoms had appeared since autumn 2021 and were diagnosed as allergic purpura. Blood tests revealed normocytic anemia [hemoglobin (Hb) 91 g/L], thrombocythemia (462 G/L), and normal leukocyte count (8.06 G/L). There were no blast cells in peripheral blood.

A repeated bone marrow biopsy, performed in January 2022 with immunophenotypic staining, did not show disease progression and did not confirm the suspicion of accelerated phase CML. Additionally, no enhancement in *BCR-ABL* transcript (≤ 0.1%) was shown. There was no enlargement of the internal organs, and antinuclear antibodies were not detected. An unclear clinical picture (including neutropenia, anemia, joint and muscle pain, skin rash, most often erythematous and maculopapular, skin inflammation, weight gain or loss, and weakness) was suggested to be a result of adverse reaction to imatinib. The medication was switched to nilotinib.

After about a month, the patient was readmitted due to swallowing difficulties, further weight loss (approx. 5 kg), oral erosions, and purpura on the lower limbs. Laboratory tests showed progress in anemia (Hb 74 g/L), leukocyte count was 9.4 G/L, thrombocythemia was 648 G/L, and serum C-reactive protein (CRP) level was 71 mg/L. The peripheral blood smear shows no signs of rejuvenation. The physical examination revealed erosions of the tongue and ulceration of the hard palate (approx. 3 cm in diameter). No pathogenic bacteria were cultured from the ulcers. Several evaluations were performed due to suspicion of a secondary malignancy. Esophagitis (classified endoscopically grade B in the Los Angeles classification) was found, and *Helicobacter pylori* infection was detected and eradicated. Computed tomography revealed sclerotic and lytic remodeling of both maxillary bones, mucosal changes in the ethmoid, maxillary, and sphenoid sinuses, amorphous calcifications inside the left orbit, fibrous and interstitial changes, and micronodules of the lungs as well as gallstones, and a cyst of the right kidney. Additionally, serum cANCA titer was 1:100.

Pathological evaluation of tissue samples from ulceration of the hard palate showed inflammatory and necrotic tissues with multiple eosinophils and multinucleated giant cells, fibrosis, and blood vessels destroyed by inflammatory infiltration. No malignant cells were found. GPA was suspected. Imatinib was restarted.

On admission to the rheumatology ward, the patient reported additional symptoms occurring for several months: pain in the knee and ankle joints with swelling, periodic night sweats, no fever, and nasal congestion. The following findings were detected: raised macular rash of the lower limbs with ulceration of the right lateral malleolus (Fig. 1), the left eye protruding, nasal obstruction, multiple mucosal ulcerations, and scabs. Computed tomography of the paranasal sinuses confirmed the previously described infiltrative changes and bone destruction (numerous defects of the nasal septum and nasal bones, thickening of the mucosa of the ethmoid cells, left sphenoid sinus, infiltration of adipose tissue of the left orbit (Fig. 2). High-resolution computed tomography of the chest showed micronodules and lung nodules, reticular changes in the lower lobes, and bilateral multiple opaque glass areas. These findings had not been demonstrated in earlier imaging evaluations (Fig. 2). Magnetic resonance imaging revealed an extensive fatty infiltration of the left orbit, causing the eyeball to move forward, and an infiltration of the soft tissues of the cheeks and fatty tissue of the lower-lateral part of the right orbit (Fig. 3). There was no significant change in primary laboratory test results but an increase in acute phase reaction. No alteration in coagulation was found either in the clinical picture or in standard laboratory tests.

The diagnosis of generalized GPA was made. The disease activity in the Birmingham Vasculitis Activity Score (BVAS) included 1 major symptom (active urine sediment) and 7 minor symptoms (purpura, skin ulcers, mouth ulcers, retrobulbar mass with exophthalmos, nasal ulceration, sinus involvement, lung nodules, and small cavities).

Medication for induction of remission was administered. It included pulses of methylprednisolone (750 mg in total), oral prednisone (40 mg/d), and the first infusion of cyclophosphamide (1000 mg).

Medication resulted in clinical improvement and a significant reduction in the concentration of inflammatory indices [a decrease in CRP concentration from 84.9 mg/L to 14.7 mg/L and erythrocyte sedimentation rate (ESR) from 96 mm/1 h to 32 mm/1 h]. The cumulative cyclophosphamide dose in October 2022 was 6.0 g, and the clinical state was improved. The patient denied joint pain, shortness of breath at rest, fever, cough, bloody discharge from the nose or ear, hemoptysis, erosions of the mouth and throat, and bleeding from the gastrointestinal tract. He only reported shortness of breath during strenuous exercise. Physical scars and discoloration from healed leg ulcers were present, but there were no new ulcers as of June 2022. Laboratory tests revealed mild normocytic anemia and moderately elevated inflammatory markers (CRP — 10.8 mg/l and ESR — 27 mm/h).

There was a slight regression. Subjectively assessed changes covered approximately 10% of the lung parenchyma in the chest high-resolution computed tomography. A former compression fracture of the L1 vertebral body was visualized. There was no worsening in functional pulmonary tests.

A computed tomography scan of the paranasal sinuses showed extensive sclerotic changes in the bony walls of the maxillary sinuses, defects in the bone structure of the thinned nasal septum, ossification in the soft tissues in the left infratemporal fossa, bilateral lysis of the inferomedial walls of the orbits, advanced infiltration of adipose tissue in the left orbit with blurred muscle contour of the extrinsic ocular muscles and optic nerve - currently without displacement of the eyeball, mucosal changes in the left and right ethmoid intensified — the frontal sinuses were completely airless.

The disease activity was assessed on the BVAS scale at 6 points (2 minor worsened symptoms: sinus involvement, bloody nasal discharge, and ulcers; four minor persistent symptoms: purpura, retrobulbar tumor with exophthalmos, nodules or lung cavities, other infiltrates secondary to vasculitis), indicating limited disease/exacerbation.

Treatment with cyclophosphamide pulses was continued to a cumulative dose of 7.0 g. Rituximab was administered. The drug was administered in November 2022 (4 doses of 500 mg i.v.). The next dose (2 infusions) was given in July 2023. Clinical and laboratory evaluation indicated a remission of GPA and a stable state of CML.

Discussion and a short literature review

Analyses of AAV, including GPA as a disorder facilitating the development of various neoplastic diseases, provide sufficient evidence to consider GPA as a disease by itself and a disease associated with management that are significant risk factors of malignancy [11]. In contrast to that description, the development of AVV in patients with established hematologic diseases is exceptionally rare.

Bîrluţiu et al. [12] described the case of a 73-year-old Caucasian man suffering from CLL for 8 years, treated with chlorambucil and prednisone, who was diagnosed with GPA. The patient reported to the Department of Infectious Diseases due to fever, weight loss, headache, double vision, and hemorrhagic nasal discharge. Physically present were: fever up to 39°C, eyelid edema, scleritis, subconjunctival hemorrhage in the left eye, swelling of the

left orbital area and left zygomatic area, epistaxis, pustular rash in the cervical and posterior thoracic region, enlarged bilateral lymph nodes axillary; hepatomegaly and moderate splenomegaly. The patient was initially treated for rhinosinusitis, and a nasal mucosa biopsy was obtained, which showed features typical of GPA. c-ANCA antibodies were also found. Meropenem, fluconazole, teicoplanin, and methylprednisolone were used in therapy, and platelet concentrate was transfused.

There are common or similar mechanisms of immune dysregulation that lead to autoimmunity and malignancy. The preservation of self-antigens from misdirected immune responses can be associated with survival and proliferation of autoreactive cellular. These phenomena result in the development of various forms of autoimmunity. Similarly, impaired immune control of the expansion of neoplastic clones can be a mechanism contributing to the development of malignancy. Autoimmunity to several autoantigens in AVV is believed to be a mechanism facilitating the initiation and progression of some hematological malignancies [11]. The concept of paraneoplastic AAV was initiated by observations of vasculitides associated with solid cancers, particularly malignant tumors of the colon and kidney [13]. Later, cases of AAV associated with underlying hematological malignancies were reported [14–16]. Most of the described cases were a diagnostic challenge due to the similarity of vasculitis symptoms to malignancy exacerbation. The incidence of vasculitis occurring in close temporal association with cancer is considered to be very low. The pathophysiological mechanism of such association remains unclear, but the role of proteinase 3 as a molecule involved in autoimmunity and malignancy has been suggested [17].

The opposite situation, the development of oncohematological disease in patients with established AAV is more common but in a significant part attributed to medication, especially cyclophosphamide medication [18].

From the point of view of clinical practice, it is important to remember that a diagnosis of a malignant disorder does not exclude the occurrence or new development of an autoimmune disease. Moreover, the symptoms and signs of both maladies may be akin, and an in-depth differential diagnosis is needed. However, it is difficult to point out the single test or test that should be performed to detect the development of vasculitis or other autoimmune disorders in patients with malignancy. The new appearance of autoantibodies can be considered as a suggestion of such disease but is not specific and may also occur in malignancy.

Summing up, the coincidence of AAV and hematological malignancies constitutes an interesting but challenging problem for clinical practice. The reported case suggests that AAV can also develop in patients with CML, which is rarely reported in the literature.

Conflict of interest.

Authors declare no conflict of interests.

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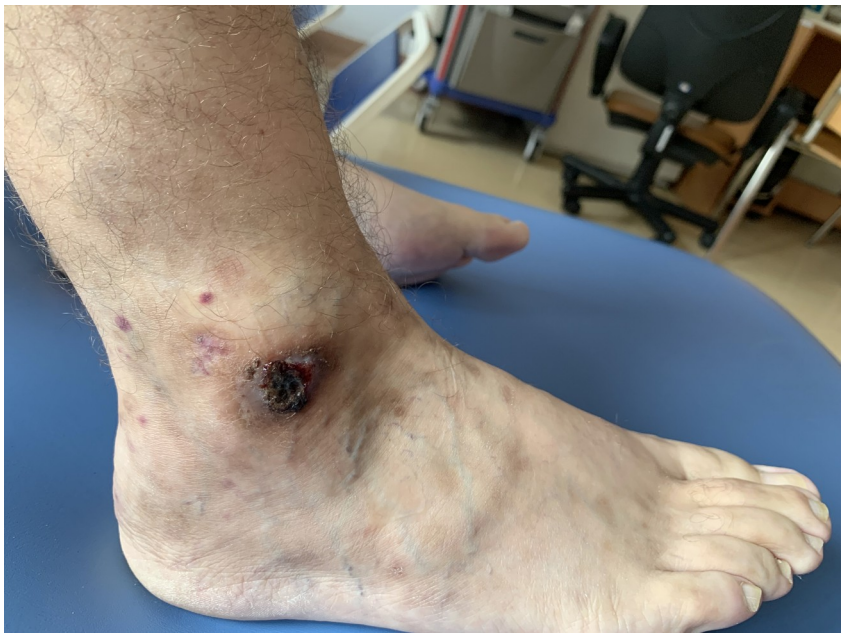

1A

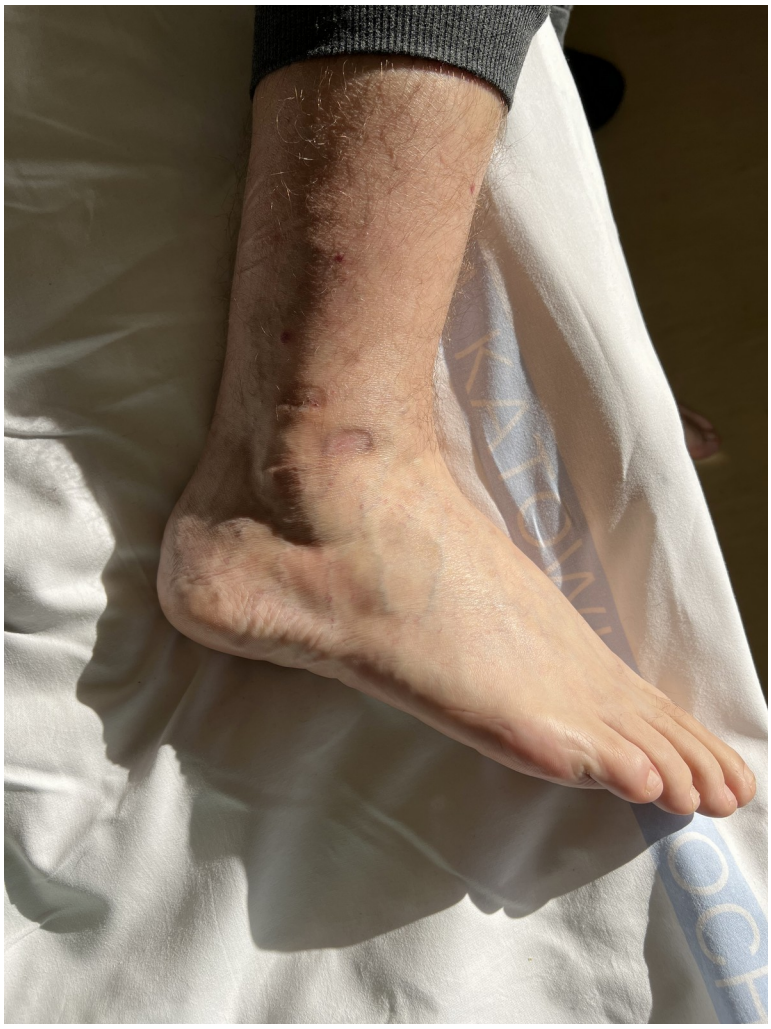

Fig. 1B

Figure 1. Ulcerations on the right legs before (**A**) and after medication (**B**)

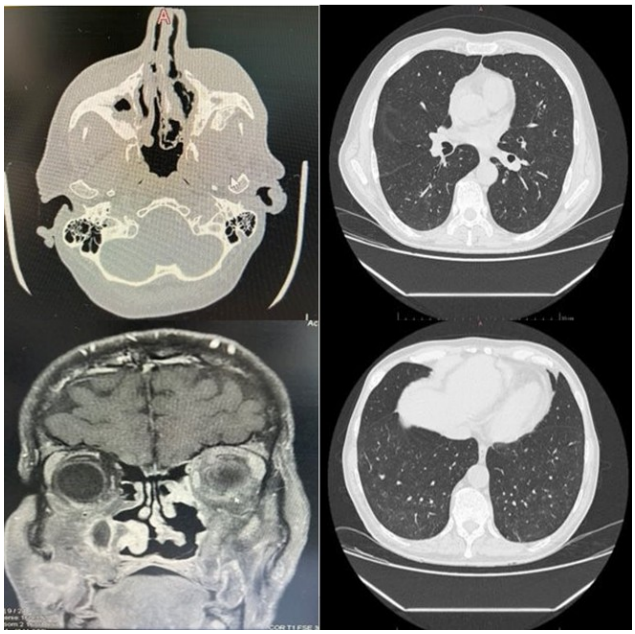

Figure 2. Computed tomography of the skull and chest

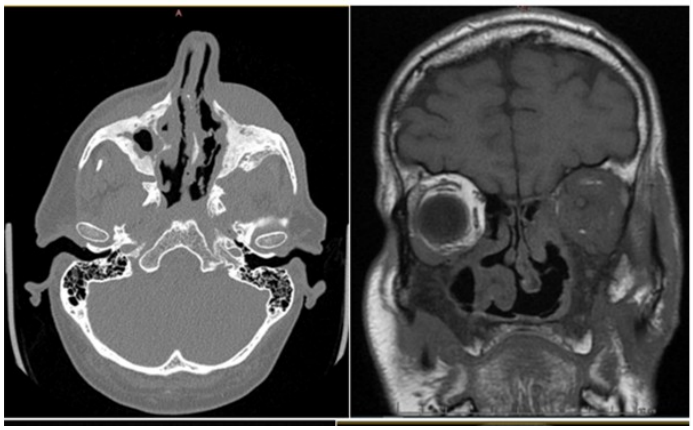

Figure 3. A fatty infiltration of the left orbit

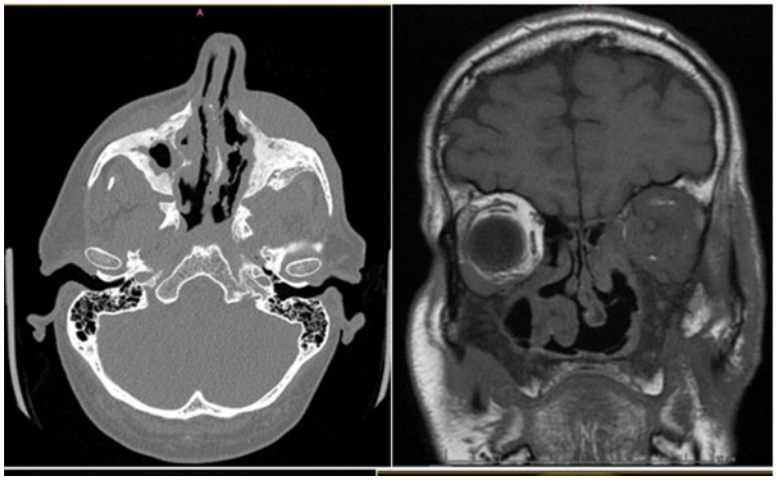

Fig. 3. A fatty infiltration of the left orbit