Emergence of acute promyelocytic leukemia in a patient with granulomatosis with polyangiitis during treatment with cyclophosphamide: a rare case report

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SUMMARY

Granulomatosis with polyangiitis (GPA) is a rare autoimmune disease that affects multiple organs and causes inflammation, necrosis, and vasculitis in small blood vessels. Treatment for GPA involves achieving and maintaining remission. In recent studies, cyclophosphamide-based regimens have been linked to comorbidity hazards, including an increased risk of malignancies, especially hematological ones. Acute myeloid leukemia is the main hematologic malignancy that can complicate GPA. In this context, we report the case of a middle-aged woman with GPA who developed acute promyelocytic leukemia (APL) during maintenance with cyclophosphamide. She was treated with all-trans retinoic acid at 50 mg/day and arsenic trioxide at 10 mg/day, along with steroids. This case highlights the unique emergence of APL in a GPA patient during cyclophosphamide therapy. A single case has previously been reported on the development of APL in a patient with GPA while using azathioprine monotherapy for 2 years.

Key words: *Acute promyelocytic leukemia, AML-M3, granulomatosis with polyangiitis, Wegener's granulomatosis, C-ANCA vasculitis, AAV.*

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INTRODUCTION

Granulomatosis with polyangiitis (GPA) is a rare autoimmune multisystemic small-vessel vasculitis pathologically characterized by an inflammatory reaction pattern (necrosis, granulomatous inflammation, and vasculitis) (1). It belongs to the anti-neutrophil cytoplasmic antibody (ANCA)-associated small vessel vasculitides involving various organs such as the nasal septum, sinuses, upper respiratory tract, lungs, and kidneys (2, 3).

The treatment of choice depends on the severity of the condition. If the patient is experiencing a life-threatening or organ-threatening clinical course, the goal is to achieve rapid and long-lasting remission. However, if the patient is not in such a critical condition, more gradual immunosuppression is used. Generally, the treatment follows a 2-step approach, which includes "remission induction" and "remission maintenance". The first step involves achieving remission, while the second step focuses on maintaining it (4).

However, cyclophosphamide-based regimens are linked to co-morbidity hazards, such as the well-known risk of treatment-induced cancer. Retrospective cohort studies and register-based analyses have been used to gauge the severity of the malignancy risk in GPA. Non-melanoma skin cancer and urinary bladder cancer incidence are increasing, while other studies have reported an increase also in leukemia incidence (5). The main hematologic malignancies associated with GPA are myelodysplastic syndrome or acute myeloid leukemia (AML) (6). To the best of our knowledge, there has only been one case reported in the literature which illustrates the development of acute promyelocytic leukemia (APL) in a GPA patient after 2 years of azathioprine monotherapy (7).

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This case was presented to highlight the unique emergence of acute promyelocytic leukemia (APL) in a middle-aged lady with GPA during remission maintenance with cyclophosphamide. Furthermore, it is important to highlight the challenges associated with managing these 2 illnesses.

CASE REPORT

A 52-year-old female patient was diagnosed with GPA in March 2022 after experiencing intermittent fever, fatigue, purpuric rash, polyarthralgia, scleritis, recurrent sinusitis, epistaxis, and otitis media, productive cough, hemoptysis, multiple cavities on high-resolution computed tomography, positive cANCA (PR 3), but no renal involvement (Figure 1).

The patient was treated with 7 doses of cyclophosphamide 500 mg every 2 weeks, following the failure of 2 doses of rituximab at 1 g, as well as high doses of steroids with both regimes, and a good response was achieved.

The patient presented to the rheumatology outpatient clinic 3 months after the last and 7th dose, complaining of pain, redness, dryness, blurred vision in both eyes and photophobia but no diplopia. She experienced nasal congestion and a frontal headache, but neither nasal discharge nor epistaxis were present. She also reported experiencing numerous uncomfortable oral ulcers but no hair loss, photosensitivity, or skin rashes. No shortness of breath was present, but there was a productive cough, hemoptysis, and pleuritic chest pain.

Her presentation was associated with polyarthralgia, intermittent fever with drenching, night sweating, and fatigability, but no weight loss. Medical history revealed hypertension, steroid-induced hyperglycemia, and two previous COVID-19 infections that were uneventful. She had no significant surgical history. Upon physical examination, her vital signs were within the normal range, apart from a sinus tachycardia of 120 bpm. She had a moonlike face. There was a pallor of the conjunctiva and palmer creases. Bilateral proptosis was present, mainly on the right side, with bilateral periorbital swelling, but no dryness and a negative Schirmer test. She had malar telangiectasia and bilateral parotid swelling measured at 2×2 cm, which were firm, not tender, and freely movable from the skin and underlying structures. Her mouth was dry; she had multiple dental caries, dental loss, and multiple oral red spots. There were multiple ecchymotic spots at the sites of cannulation in the forearms.

A diminished chest expansion of 4 cm was observed during the respiratory examination, with bronchial breathing in the left middle zone and normal vesicular breathing on the right side.

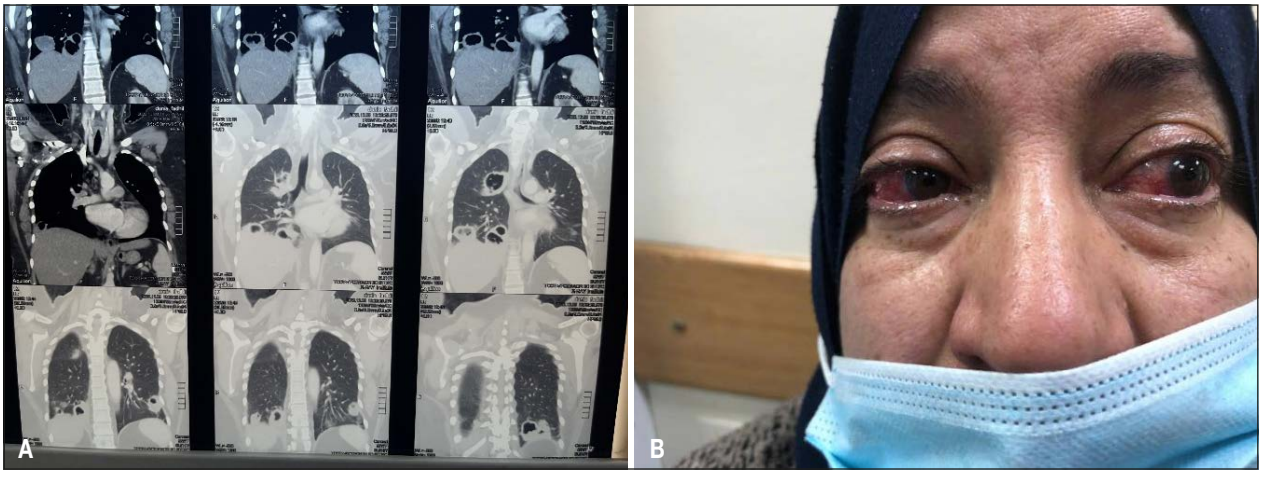

Figure 1 - A) Computed tomography scan showing multiple cavitary lesions of the lungs surrounded by minimal consolidation; B) photo of the patient's eyes at admission.

A symmetrical abdominal distention that was freely moveable with respiration was observed. There were multiple vertical striae, each 2 cm in width, of a light pink color; the liver was palpable with a span of about 17 cm and no splenomegaly.

The evaluation revealed no abnormalities in the cardiovascular, neurological, or musculoskeletal systems.

Laboratory investigations showed pancytopenia with a white blood count of 0.59×10^3/μL (normal reference: $4\text{-}10\times10^3$/μL), a neutrophil count of 0.17×10^3/μL, and a lymphocyte count of 0.37×10^3/μL, hemoglobin level of 8.6 g/dL (normal reference: 12-17 g/dL), platelet count of 63×10^3/μL (normal reference: $150\text{-}450\times10^3$/μL), and blood film revealing 2% leukemic promyelocytes with a tendency for rouleaux formation as shown in Figure 2. A high erythrocyte sedimentation rate of 111 mm/h (normal 0-20 mm/h) and a raised C-reactive protein of 103 mg/L (normal 0-10 mg/L) were present. Lactate dehydrogenase was 316 U/L (normal 81-234 U/L). The renal, liver, and urinalysis results were all normal. The antinuclear antibody, the anti-double stranded DNA, and the anti-Ro and La antibodies were negative. C3 levels of 250 mg/dL and C4 levels of 57 mg/dL were elevated.

Abdominal ultrasound showed liver enlargement measured at 17.5 cm, with increased echogenicity marking fatty infiltration with homogeneous texture and no focal lesion.

The patient was referred to the hematology department for further evaluation, where bone marrow examination revealed faggot cells with Auer rods (Figure 2) with infiltration by hypergranular leukemic promyelocytes, which formed 65% of the absolute neutrophil count (ANC). Blast cells make up 1-2% of ANC. Flow cytometry immunophenotypic analysis of the bone marrow was compatible with acute promyelocytic leukemia-variant with both neutrophilic and basophilic maturation. It revealed the presence of distinct cell clusters in the lower granulocyte region on the CD45/side scatter (SSC), with moderate CD45, low to intermediate SSC signal, and forward scatter, with the majority of cells falling into the medium- to large-size cell range and residual lymphocytes seen in their respective regions. These findings, together with the positive *PML-RARA* gene *t*(15;17) fusion results, corroborated the diagnosis of APL. Hence, the emergence of APL in this patient while undergoing remission maintenance with cyclophosphamide, which was administered for her primary condition, GPA, required discontinuation of cyclophosphamide and initiation of treatment for APL using the therapeutic regimen of all-trans retinoic acid (ATRA) 50 mg/day and arsenic trioxide (ATO) 10 mg/day for remission

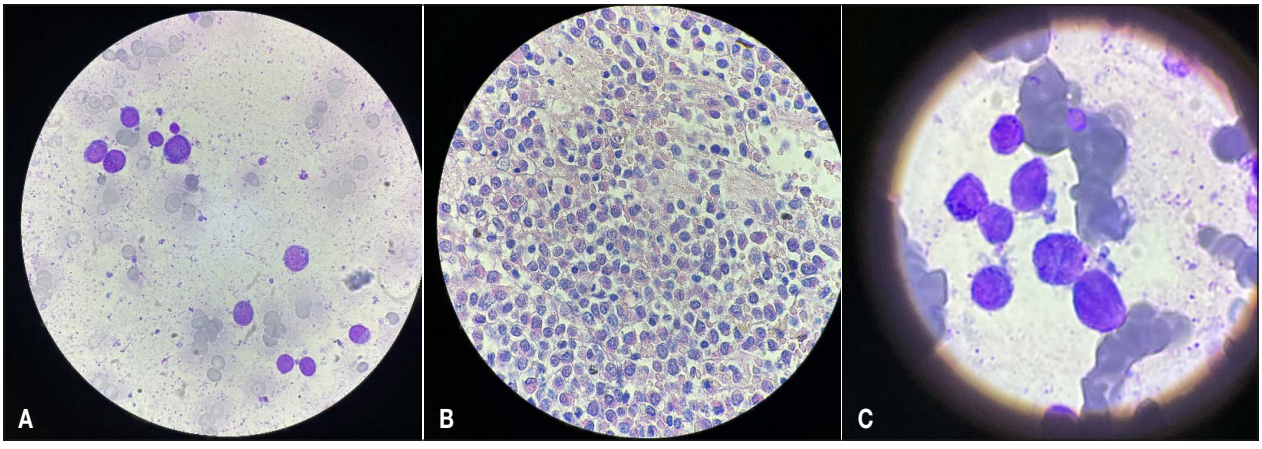

Figure 2 - A) Bone marrow aspiration shows infiltration by leukemic promyelocytes (hypergranular) forming 65% of absolute neutrophil count; B) faggot cells are seen; C) bone marrow biopsy shows diffuse infiltration by primitive cells (promyelocytes) with suppressed other hemopoietic elements.

induction, along with dexamethasone 8 mg/day, and then replaced by 30 mg/day of prednisolone with gradual tapering. The steady improvement in the patient's condition over the 3-week period following her admission was testified by the resolution of her scleritis and the restoration of an usual blood profile. The patient has been assigned to undergo monthly surveillance.

DISCUSSION AND CONCLUSIONS

The term GPA, as opposed to Wegener's granulomatosis, describes the main pathologic feature of granulomatous inflammation with vasculitic involvement of multiple types of vessels (polyangiitis) (8). The respiratory system is the one that is most frequently impacted by GPA; in addition, half of the patients have early ocular involvement, with the main complaint being deep boring pain with erythematous tender eyes, seen as areas of capillary nonperfusion on ocular examination. Moreover, epistaxis, sinusitis, serous otitis media, and nasal or mouth ulcers are also common (9). Scleritis is reported to be the presenting sign of GPA, while in other patients, it occurs despite the patient being in remission, and it is the 3rd most common ocular manifestation following orbital and nasolacrimal involvement (10).

AML has an increased risk of developing in a patient with an autoimmune disease, including rheumatoid arthritis, ulcerative colitis, and systemic vasculitis, with the latter having the largest increase in risk. A meta-analysis has shown an increased risk of developing malignancies, particularly leukemia, non-melanoma skin cancer, and bladder cancer, in patients with ANCA-associated vasculitis after being treated with cyclophosphamide. The risk increased because the long-term survival rate of these patients has improved. GPA patients experience a greater-than-expected number of specific malignancies after traditional immunosuppressive therapies; furthermore, combining TNF inhibition with cyclophosphamide may increase the risk of malignancy beyond the risk observed with cyclophosphamide treatment alone (11).

APL, a subtype of AML, is recognized by the fusion of the promyelocytic gene with the *RARA* genes *t*(15;17), and the generation of the new *PML-RARA* (12).

The diagnosis of GPA in our patient was reached based on the American College of Rheumatology/European League Against Rheumatism criteria, where the patient showed positive test results for c-ANCAs and anti-proteinase 3, cavitation on chest imaging, nasal involvement as bloody nasal discharge, left ear hearing impairment and redness of both eyes, achieving a score of 12 points. Five points are sufficient to classify the patient (13). Remission induction of GPA consists of a combination of high-dose corticosteroids with either cyclophosphamide or rituximab (4). Several studies have addressed the effects of different treatment regimens to reduce the risk of developing malignancies, particularly cyclophosphamide-induced toxicity. Relapse may also be noted and is sometimes heralded by rising c-ANCA titers, and mortality due to GPA has been significantly decreased due to the use of cytotoxic therapy with cyclophosphamide and glucocorticoids (14).

Methotrexate (MTX) is an appropriate alternative to cyclophosphamide to obtain remission in patients with early limited-type ANCA-associated vasculitis (AAV) and normal renal function. This avoids cyclophosphamide exposure and its long-term consequences (4). A randomized control trial has shown that the use of MTX as opposed to cyclophosphamide can lead to similar clinical results in patients with limited AAV. However, cyclophosphamide yields better results in patients with extensive disease manifestations, such as multiple pulmonary granulomas (15).

To the best of our knowledge, the coexistence of APL and GPA has only occasionally been mentioned in the literature, and on these few occasions, the incidence occurred after using cyclophosphamide for the maintenance phase of the treatment of GPA (6). Prior to admission, the patient had been well-controlled on cyclophosphamide and a

tapering regimen of prednisolone. She then experienced recurring scleritis with nasal congestion, and a frontal headache. She also reported experiencing numerous uncomfortable oral ulcers. Her presentation was associated with polyarthralgia, intermittent fever with drenching, night sweating, and fatigability, but no weight loss was evident. Along with spontaneous skin ecchymosis, her complete blood picture revealed pancytopenia. The clinical picture thus supported a GPA relapse, and the reason for pancytopenia was investigated afterward. We listed 3 relevant possible diagnoses for pancytopenia: hematological malignancy, concomitant systemic lupus erythematosus, and drug-induced pancytopenia. The serological test results for lupus were negative, but the hematological examination supported the diagnosis of APL. Consequently, it may be inferred that drug-induced pancytopenia has been ruled out. She was given ATRA 50 mg/day and ATO 10 mg/day as maintenance therapy for APL with the lowest possible dose of oral prednisolone for GPA. This was done after the laboratory and pathology results of the bone marrow biopsy confirmed the diagnosis, and immunohistochemistry showed a *t*(15;17) fusion of *PML-RARA* genes. A gradual improvement in her condition has been observed over the following 3 weeks after admission; she is clinically asymptomatic with the disappearance of scleritis and a normal blood picture. She was discharged from the hospital to be monitored monthly.

Contributions
All the authors made a substantial intellectual contribution, read and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

Conflict of interest
The authors declare that they have no competing interests, and all authors confirm accuracy.

Ethics approval and consent to participate
No ethical committee approval was required.

Patient consent for publication
The patient gave her informed consent.

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Availability of data and materials
Data available from the corresponding author upon request.

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