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Development of Acute Promyelocytic Leukemia in a Patient with Granulomatosis with Polyangiitis: A Case Report

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Granulomatosis with polyangiitis (GPA) is a rare disorder of unknown etiology, which is characterized by necrotizing granulomatous inflammation of the upper respiratory system and kidneys. Immunosuppressive treatment (cyclophosphamide or azathioprine with glucocorticoids) improved the outcome of GPA, however, latent comorbidity (cancers and hematologic malignancies) has become more prevalent in recent years. Here, we present a first case of the patient with GPA complicated by acute promyelocytic leukemia (APL) successfully treated with molecular-targeted therapy. A 77-year-old female was referred to our hospital for nasal obstruction, hearing loss, and fever. Otorhinolaryngological investigation revealed otitis media, and head computed tomography (CT) showed paranasal mucosal thickening with septal perforation. Chest CT showed cavitary granulomatous lesions in both lungs. Biopsy of the nasal mucosa revealed granulomatous lesions, and the patient was finally diagnosed with GPA. Oral administration of prednisolone 50 mg/day was initiated, and oral azathioprine (50 mg/day) was added. After 26 months of azathioprine initiation, pancytopenia developed and azathioprine was stopped. Then sudden elevated levels of blasts appeared in the hemogram (blasts 11%). She was diagnosed with APL via bone marrow examination which revealed plenty of faggot cells with Auer rods and chromosomal mutation. The patient was started on all-trans retinoic acid 60 mg/day following arsenic trioxide 7 mg/day in consideration of elderly onset. Complete remission was achieved and oral prednisolone was successfully reduced to 15 mg/day without a major relapse of GPA. Because GPA can be complicated by APL even during maintenance treatment using azathioprine, careful monitoring should be performed in such patients.

Keywords: acute promyelocytic leukemia; all-trans retinoic acid; azathioprine; granulomatosis with polyangiitis; hematologic malignancy
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Introduction

Granulomatosis with polyangiitis (GPA) is a rare disorder of unknown etiology, which is characterized by necrotizing granulomatous inflammation of the upper respiratory system and kidneys (Leavitt et al. 1990). GPA is a type of systemic anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), which also includes microscopic polyangiitis and eosinophilic GPA (Jennette et al. 2013; Jennette and Falk 2014). These diseases exhibit necrotizing vasculitis with the absence or paucity of immune deposits and predominant involvement of small vessels, including capillaries, venules, arterioles, and small arteries (Jennette et al. 2013; Jennette and Falk 2014). However, hematological manifestation is usually not observed in GPA, except for inflammatory reactions.

The use of immunosuppressive agents with glucocorticoids, especially cyclophosphamide (CYC) for remission induction or azathioprine (AZA) for maintenance therapy, improved the prognosis of patients with AAV (Fauci et al. 1983; Pagnoux et al. 2008). A recent study also revealed that additional immunosuppressive therapy improved out-

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comes even in elderly-onset AAV (≥ 75 years old) (Sato et al. 2018). Late comorbidity, including cancer, has become more prevalent in recent years as survival rates have improved (Knight et al. 2002, 2004; Ahn et al. 2019; Yashiro-Furuya et al. 2022). Recent studies describe that GPA may be complicated with malignancies, including leukemia (Westman et al. 1998; Ramadan et al. 2012; Shang et al. 2015), and cytotoxic agents, such as CYC, can cause hematological malignancies (Faurschou et al. 2008; Knight et al. 2015).

The main hematologic malignancies complicated by GPA patients are myelodysplastic syndrome or acute myeloid leukemia (AML) (Knight et al. 2015). Acute promyelocytic leukemia (APL) is a specific type of AML (identified as AML-M3 by the French-American-British classification) associated with the fusion of promyelocytic (*PML*) gene with the retinoic acid receptor *α* (*RARA*) gene (*PML-RARA*) generated by the t(15;17) translocation. Previously, APL was highly fatal because of bleeding complications. By contrast, recent molecular-targeted therapy (all-trans retinoic acid: ATRA) significantly improved the outcome of APL (Wang and Chen 2008; Ma et al. 2016). Arsenic trioxide (ATO) therapy also contributed to the improvement of the clinical outcome of this disease (Wang and Chen 2008). So far, complication with APL in patients with GPA has not been described. We present herein a rare case of a patient with GPA complicated by APL that was successfully treated with glucocorticoids and molecular-targeted therapy, including ATRA.

Case Presentation

A 77-year-old female was referred to our hospital for nasal obstruction, hearing loss, and fever. These symptoms improved with 10 mg/day of oral prednisolone (PSL), but her symptoms relapsed after PSL tapering. Otorhinolaryngological investigation revealed otitis media, and head computed tomography (CT) demonstrated paranasal mucosal thickening with septal perforation (Fig. 1A). In August 2015, she developed a fever, and a chest CT showed granulomatous lesions in both lungs, thus prompting referral to our department on the suspicion of GPA. On admission, her body temperature was 36.8°C, heart rate was 72

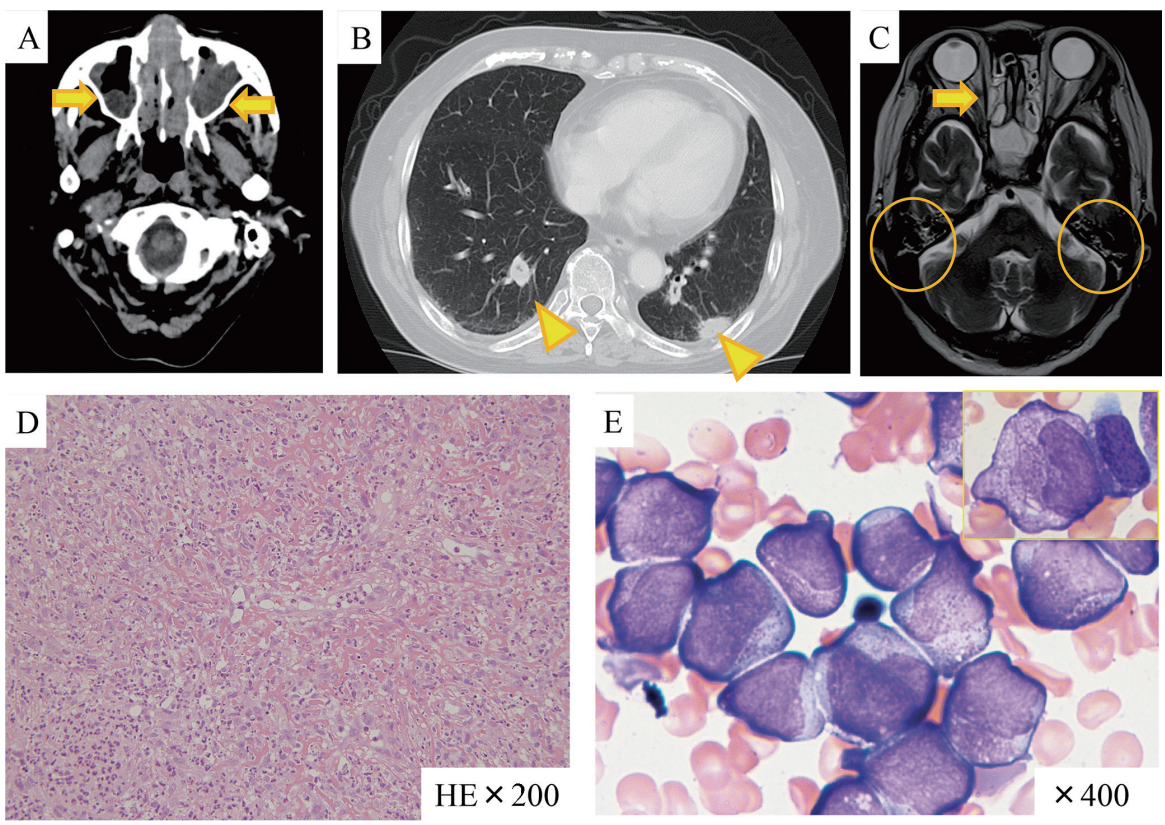

Fig. 1. Clinical images and bone marrow findings of the patient.
(A) Head computed tomography (CT) showed diffuse mucosal thickening and anterior septal perforation in the paranasal sinuses (arrows). (B) Chest CT showed granulomatous lesions with cavities in both lungs (arrowheads). (C) T2-weighted magnetic resonance imaging (MRI) showed diffuse mucosal thickening and anterior septal perforation in the paranasal sinuses (arrows). Head MRI also showed hyperintensities in the middle ear and mastoid cells, indicating bilateral mastoiditis (circles). (D) Nasal sinus tissue (200 × magnification) showed that granulation tissue was formed with a high infiltrate of neutrophils and inflammatory cells. Eosinophilic material has advanced into the perivascular space, indicating fibrinoid necrosis. (E) May-Giemsa staining (400 × magnification) revealed the presence of faggot cells with Auer rods (upper-right) in bone marrow tissue, indicating the presence of acute promyelocytic leukemia.

bmp, and blood pressure was 96/58 mmHg.

Chest CT showed cavitary granulomatous lesions (Fig. 1B), while T2-weighted magnetic resonance imaging of the head showed hyperintensity in the paranasal sinuses and bilateral mastoid cells (Fig. 1C). Laboratory examination revealed a decrease in albumin levels (2.4 g/dL) and elevation of C-reactive protein levels (7.73 mg/dL). Proteinase-3 (PR3)-ANCA and myeloperoxidase-ANCA were all negative. Urinalysis showed no proteinuria and hematuria. Biopsy of the nasal mucosa revealed granulomatous lesions (Fig. 1D), and the patient was finally diagnosed with GPA according to the American College of Rheumatology criteria (Leavitt et al. 1990) and new criteria (Robson et al. 2022). Oral administration of PSL (50 mg/day) was initiated, after which her symptoms significantly improved. CYC administration was recommended but the patient refused because she was concerned about the adverse events. She was discharged after tapering the PSL dose to 30 mg/day, and then oral AZA (50 mg/day) was added in March 2016.

On May 2018, pancytopenia occurred, prompting us to discontinue AZA. However, the pancytopenia persisted, and sudden elevated levels of blasts appeared in the hemogram (blasts 11%). After referral to the Department of Hematology, she was diagnosed with APL via bone marrow examination which revealed plenty of faggot cells with Auer rods (May-Giemsa staining, Fig. 1E) and chromosomal mutation t(12;17;15). The patient was started on ATRA 60 mg/day in May 2018 for remission induction, and ATO 7 mg/day was added considering her older age and frailty. Complete remission was achieved and tamibarotene 8 mg/day was administered for maintenance therapy. Tamibarotene was finished in May 2020 without relapse of APL. Oral PSL was gradually reduced to 10 mg/day without a major relapse of GPA for almost one year: however, as the fever and elevated CRP levels persisted in April 2019, we suspected minor flare of GPA. Then she received increased dose of PSL for 15 mg/day and kept stable condition (Fig. 2).

Informed consent was obtained from the patient. Because of a case report of single patient, ethical approval was waived for institutional review board in Fukushima Medical University.

Discussion

This patient developed APL during the maintenance therapy of GPA using AZA, without history of CYC treatment. She received ATRA following arsenic trioxide for APL treatment with glucocorticoids and resulted in good outcome without major relapse of APL as well as GPA. To the best of our knowledge, this is the first case of GPA complicated by APL successfully treated with molecular-tar-

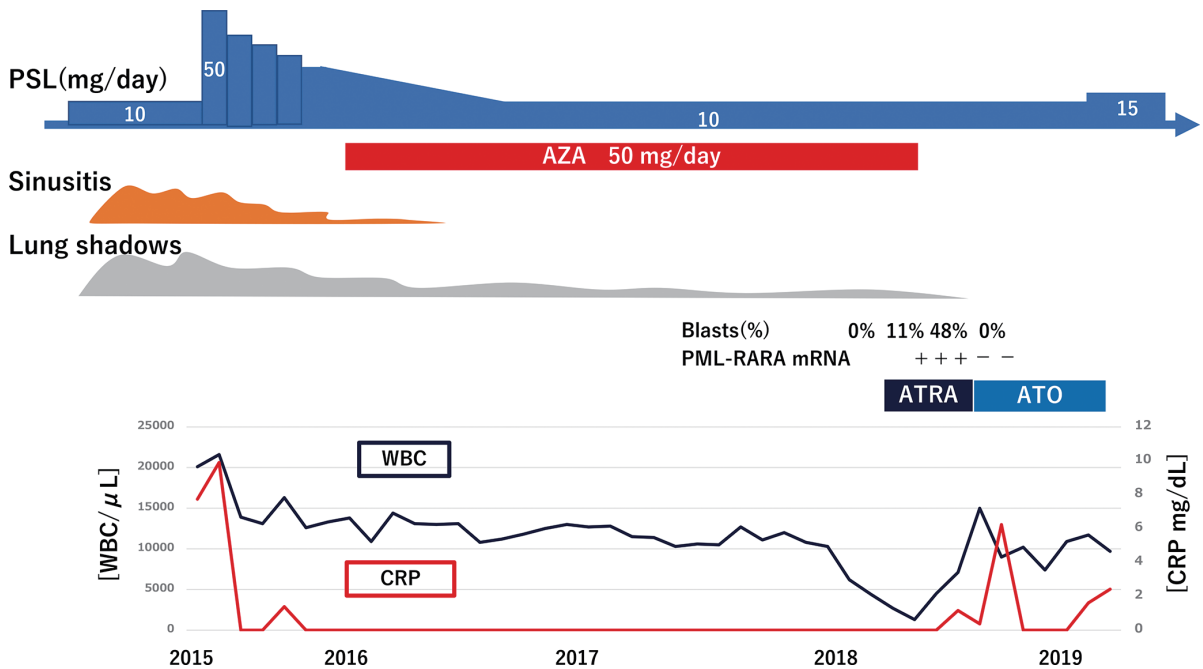

Fig. 2. Clinical course of the patient.
After diagnosis of granulomatosis with polyangiitis (GPA), she received oral prednisolone (PSL) and maintenance therapy using azathioprine (AZA). After 26 months of AZA administration, she suddenly suffered acute promyelocytic leukemia (APL). Elevated expression of promyelocytic leukemia-retinoic acid receptor alpha (PML-RARA) mRNA was detected using real-time PCR in bone marrow fluid. She received all-trans retinoic acid (ATRA) and following arsenic trioxide (ATO) for remission induction of APL. After ATRA/ATO treatment, the expression of PML-RARA mRNA in bone marrow was completely disappeared, and no further relapse of APL occurred.
ATRA, all-trans retinoic acid; ATO, arsenic trioxide; AZA, azathioprine; CRP, C-reactive protein; PML-RARA, promyelocytic leukemia-retinoic acid receptor alpha; PSL, prednisolone; WBC, white blood cells.

geted therapy (ATRA) and glucocorticoids. The complication of AML in collagen vascular disease is relatively rare.

Recent reports have indicated that increased risk of malignancy was observed in collagen vascular diseases including AAV patients (Ahn et al. 2019; Treppo et al. 2022). In Italy, Treppo et al. (2022) have described that the cumulative cancer incidence of 10 years follow-up was 8.5% in patients with collagen vascular diseases including idiopathic inflammatory myositis, Sjogren's syndrome, systemic lupus erythematosus (SLE) and systemic sclerosis. The most common cancer sites/types were breast, lung, colon, and non-Hodgkin lymphoma. Furthermore, Ramadan et al. (2012) have reviewed the existing reports on AML development in patients with autoimmune diseases. They have described that the patients with autoimmune diseases had increased risk of AML (odds ratio: OR 1.29) or MDS (OR 1.50). AML risk was significantly associated with autoimmune diseases such as rheumatoid arthritis (RA) (OR 1.28), SLE (OR 1.92), ulcerative colitis (OR 1.72), and systemic vasculitis (OR 6.23). Interestingly, APL development was frequently observed among patients with multiple sclerosis who received mitoxantrone treatment (Ramadan et al. 2012). Among these patients, they discussed a possible leukemogenic mechanism as well as evidence supporting the association of their primary immunosuppressive condition with their exposure to specific therapies (cytotoxic agents such as CYC and mitoxantrone). However, the precise pathophysiology underlying autoimmune diseases and its connection to carcinogenesis remains unclear. Nevertheless, a previous meta-analysis has described that ANCA-associated vasculitis was associated with increased cancer risk (Shang et al. 2015). In addition, Ahn et al. (2019) reported the risk of cancers in Korean AAV patients: The overall risk of cancers was significantly higher in AAV (standardized incidence ratios: SIR 1.90). Especially, the risk of lung cancers (SIR 2.23) and hematological malignancies (SIR 11.39) were higher in AAV patients.

Interestingly, recent review article described the key role of PR3, a bactericidal protein expressed by neutrophilic granules and on their plasma membrane, in the development of hematologic malignancies in GPA patients (Folci et al. 2019). Clinical studies have shown that worse clinical outcome when PR3 is present in the tumor microenvironment, partially due to the potentiation of tumor angiogenic properties (Yang et al. 2018). In fact, PR3-derived PR1 peptide is investigating as an immunotherapy target in leukemia and multiple myeloma. Taken together, PR3 can be associated with the onset of hematologic malignancy in GPA patients. However, our case was negative for PR3-ANCA upon onset of GPA. Further investigation is needed to clarify the relationship between PR3 and hematologic malignancy.

On the other hand, Knight et al. (2015) have reported the complication of hematological malignancies arising among Swedish patients with GPA from 1964 to 2012. Among 3,224 patients with GPA, 21 developed hematological malignancies, including 16 patients with myelodysplastic syndrome (MDS)-AML or AML, whereas no cases of APL were found. The median time from GPA diagnosis to hematological malignancy was 8 years (range: 5-21 years). Persistent GPA activity was observed in one case despite being under treatment for AML. The median overall survival in AML cases showed shortest (4 months, range: 0.25-12 months) in contrast to MDS (12 months, range: 2-12 months). Notably, these patients with GPA all received high cumulative doses of CYC (median 96.5 g, range 9-233 g) for a long period (median 57 months, range 6-228 months). Another previous report has indicated that alkylating agents such as CYC can initiate the development of hematological malignancy in patients with GPA (Faurschou et al. 2008).

In our case, CYC was not administered, but AZA was used for almost 2 years. Accordingly, a previous report has described the cancer risk associated with AZA use in autoimmune diseases (Ertz-Archambault et al. 2017). They described that AZA exposure was associated with a 7-fold risk for hematologic malignancies. Not only GPA, several autoimmune diseases such as autoimmune hepatitis, Crohn's disease, inflammatory bowel disease, polyarteritis nodosa, polymyalgia rheumatica, RA and SLE, have been reported to be complicated with hematologic malignancies under AZA exposure. The leukemogenic mechanism of cytotoxic agents can be explained by nonrepaired DNA

Table 1. Reported cases with exposure to azathioprine (AZA) in patients with granulomatosis with polyangiitis (GPA) complicated by hematologic malignancies.

No. Author/year	Age/sex	AZA monotherapy	Additional therapies	Duration of AZA exposure	MDS/AML diagnosis, year	Treatment for hematologic malignancies	Last follow-up (year)	Outcome
1. Ertz-Arhambault/2006	ND/F	No	CYC	19 months	AML 2007	ND	2007	ND
2. Ertz-Arhambault/2004	ND/ND	No	CYC	2 years	MDS 2008, AML 2013	ND	2013	ND
3. Ertz-Arhambault/2005	ND/F	No	CYC, MTX	1 year	MDS 2008	Decitabine	2009	ND
4. Our case/2015	77/F	Yes	No	26 months	AML (APL) 2018	All-trans retinoic acid, arsenic trioxide	2021	Alive

Reference: No. 1-3, Ertz-Archambault et al. 2017.

AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; AZA, azathioprine; CYC, cyclophosphamide; MDS, myelodysplastic syndrome; MTX, methotrexate; ND, not described.

double-strand breaks that form highly mutagenic DNA bases. Several factors including exposure time from cytotoxic therapy and previous cytotoxic therapy might also be important for the development of myeloid neoplasms (Ertz-Archambault et al. 2017). In line with this, Ertz-Archambault et al. (2017) have described hematologic malignancies in patients with GPA. Table 1 summarizes cases of AZA exposure in patients with GPA complicated by myeloid neoplasms reported in the literature, including our case. Of note, three of the four cases had a history of CYC exposure before AZA administration; only one patient (our case) received AZA monotherapy. The exposure to AZA lasted approximately 1-2 years. Three of the four patients developed AML, but treatment data were lacking for the previous cases. In any case, further investigation may be required to clarify the relationship between AZA exposure and the development of hematologic malignancy.

The chemotherapy for APL was effective in our case, but these treatments seem to have no effect on the clinical course of GPA. The patient still needed to receive PSL for the suppression of mucosal inflammation. Further accumulation of such cases is needed to clarify the association between GPA and hematologic malignancies, including APL.

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Conflict of Interest

The authors declare no conflict of interest.

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