Leukemia and Myelodysplastic Syndrome in Granulomatosis with Polyangiitis: Subtypes, Clinical Characteristics, and Outcome

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ABSTRACT. ***Objective.*** Previous studies have shown that patients with granulomatosis with polyangiitis (GPA) have an increased risk of hematological malignancies, especially leukemia. Our aim was to assess clinical characteristics and treatment of patients with GPA complicated by hematological malignancies with focus on leukemia and to describe these malignancies in more detail.

Methods. From the Swedish population-based patient register, all individuals with a diagnosis of GPA from 1964–2012 were identified (n = 3224). Through linkage with the Swedish Cancer Register, we searched for all cases of leukemia [International Classification of Diseases (ICD) 7: 204–207 and corresponding codes ICD 8–10] registered after the first discharge listing GPA. The GPA diagnosis was evaluated using the European Medical Association classification algorithm. To confirm the hematological malignancy, all diagnostic bone marrow samples were reclassified. Clinical data of both the GPA and hematological malignancy were collected from medical files.

Results. Twenty-one cases were identified, all of myeloid origin, including 9 with myelodysplastic syndrome developing to acute myeloid leukemia (MDS-AML), 7 AML, 3 MDS, and 2 chronic myeloid leukemia. The median time from GPA diagnosis to hematological malignancy was 8 years (range 5–21). All patients had severe generalized GPA and had received high doses of cyclophosphamide (CYC; median cumulative dose 96.5 g). Cytopenia occurred in 76% of the patients prior to the hematological malignancy.

Conclusion. The findings emphasize the longterm risk of leukemia and MDS in CYC-treated, severely ill patients with GPA. Cytopenia during the course of GPA may be a warning sign and warrants a liberal attitude toward bone marrow examination. (First Release Feb 1 2015; J Rheumatol 2015;42:690–4; doi:10.3899/jrheum.141104)

Key Indexing Terms:
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Granulomatosis with polyangiitis (GPA), formerly Wegener granulomatosis, is a systemic disease with no sex preference, characterized by granulomatous inflammation and necrotizing vasculitis of small- and medium-sized vessels most frequently of the upper and lower airways and kidneys, but possibly affecting any organ system. Hematological manifestations, other than signs of inflammation, are generally not observed in GPA[1]. Untreated, the disease has a fatal outcome in about 80% of cases during the first year after diagnosis[2]. However, after the introduction in the 1970s of cyclophosphamide (CYC) together with systemic corticosteroids (CS) as standard therapy for induction of remission[3], survival greatly improved. Since the improved survival, late comorbidity and longterm side effects of the disease and of its treatment have become increasingly clinically relevant. An increased incidence of cancer in GPA has been repeatedly reported[4,5,6], including a 2.5–33 times increased risk for bladder cancer[6,7,8,9,10,11]. Several studies have also suggested an increased risk for hematological malignancies[6,7,9,10,11,12]. In a previous Swedish study of malignancy in GPA, the risk of leukemia was increased 6-fold compared to the general population[6]. In a Danish study, a 19-fold increase in risk was noted for acute myeloid leukemia (AML) in patients with GPA who received CYC in comparison to the general population. However, this was

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based on only 3 cases of AML in the cohort[7], and detailed characteristics of patients with GPA developing leukemia and the characteristics and prognosis of these leukemia were not described.

Our objective was to assess clinical and treatment characteristics of patients with GPA complicated by hematological malignancy with focus on leukemia, as well as to describe type and prognosis of the hematological malignancy, using a large cohort of patients registered with a diagnosis of GPA in the Swedish patient register.

MATERIALS AND METHODS

The Swedish population-based patient register contains information, based on the individual national registration number (NRN), on all inpatient care since 1964 with nationwide coverage since 1987 and similarly nonprimary outpatient care since 2001[13,14]. From this register, we identified all individuals discharged with the diagnosis GPA [n = 3224; International Classification of Diseases (ICD) 446.2, 446E, M31.3] as the main or contributory diagnosis between 1964 and 2012.

Using the NRN, we linked the cohort to the Swedish Cancer Register that, because of the mandatory reporting from both clinicians and pathologists, has a completeness of around 98%[15]. Through this linkage, we obtained information on all leukemia (myeloid and lymphatic; ICD 7: 204–207 and corresponding codes in ICD 8–10) registered after the first discharge listing GPA (n = 37).

To evaluate the GPA diagnosis, we scrutinized the medical files of all patients using the European Medicines Agency vasculitis classification algorithm[16] that incorporates the American College of Rheumatology criteria[17,18], the Chapel Hill Consensus Conference[19], as well as surrogate markers in the classification. Cases whose records contained insufficient information for validation (n = 2) or did not fulfill the criteria for GPA according to the algorithm (n = 12) were excluded. Most of the excluded cases had another vasculitis (microscopic polyangiitis, eosinophil granulomatous polyangiitis, and giant cell arteritis); some had other systemic inflammatory diseases, progressive glomerulonephritis, or had erroneously been registered under GPA diagnosis during investigation of an inflammatory condition. Further, we excluded cases in which the hematological malignancy was found to precede the onset of GPA (n = 1), as well as those in which the hematological malignancy could not be confirmed (n = 1).

The bone marrow samples and slides of the remaining cases were collected from the respective pathology departments, and 1 experienced hematopathologist (CS) classified the malignancies according to the World Health Organization classification[20]. Clinical data of both the GPA and the hematological malignancy were collected from the medical records from onset of GPA until death or December 31, 2012. Antineutrophil cytoplasmic antibody (ANCA) status was extracted up to 1 year before hematological diagnosis. Disease activity at GPA diagnosis was evaluated retrospectively using the Birmingham Vasculitis Activity Score (BVAS), version 3.0[21,22]. The Vasculitis Damage Index (VDI) is a cumulative score adding damage caused by disease or treatment (or unrelated) over time[23,24,25] and was assessed at the time of diagnosis of hematological malignancy.

As a further approximation of disease burden and intensity, we aimed at assessing remission periods in relation to total disease course. However, neither the information in the medical files nor the nature of the disease allowed stringent retrospective calculation of remission periods.

To study whether bone marrow depression, manifested as periods of cytopenia during the course of GPA, might be associated with subsequent hematological malignancy, information regarding blood counts was extracted from the medical files. Because reference values for anemia and other cytopenia have varied over time and between different laboratories, we consistently used the following definitions for cytopenia: anemia (S/P-hemoglobin < 110 g/l), leukopenia (S/P-leukocytes < 3×10^9/l), and thrombocytopenia (S/P-platelets < 130×10^9/l). Values less than a year prior to the diagnosis of the first hematological malignancy were ignored to avoid confusion with the yet undiagnosed malignancy.

Additionally, collected data included cytogenetic analyses, when performed, and treatment of the GPA disease. Overall survival from hematological malignancy diagnosis was estimated from the date of diagnosis according to the cancer register until December 31, 2012, at the latest.

Ethical approval was obtained from the Regional Ethical Review Board in Uppsala.

RESULTS

GPA disease characteristics. In total, 21 cases with GPA and hematological malignancy were identified. The median age at GPA diagnosis was 58 years (range 25–69) and 16 of the patients were male (75%; Table 1). Sixteen of the cases were ANCA-positive by immunofluorescence, ELISA, or both[26,27]. ANCA status was unknown in the 5 cases diagnosed from 1968 to 1982 (i.e., prior to the era of ANCA testing). All cases had undergone diagnostic biopsy revealing granulomas and/or unspecific inflammation, leukocytoclastic vasculitis, necrosis, histiocytosis, and giant cells. The 9 kidney biopsies all showed signs of glomerulopathy and/or crescent nephritis.

All patients had a generalized and severe GPA disease with a median BVAS at GPA diagnosis of 21 p (range 11–36) and with a median of 5 involved organ categories including general manifestations with myalgia, arthralgia/arthritis, fever > 38°C, or weight loss (≥ 2 kg). The most common organ involvement was the ear, nose, and throat, followed by renal disease and mucous membranes/eyes.

Table 1. Characteristics of patients with GPA who developed a hematological malignancy.

Cases	Total, n = 21
Male, n (%)	16 (75)
Female, n (%)	5 (25)
Age at GPA onset, yrs, median (range)	58 (25–69)[1]
ANCA-positive ever, n (%)	16/16 (100)[2]
c-ANCA or PR3-ANCA	12
ANCA of unspecified type	2
P-ANCA or MPO-ANCA	2
Cytopenia > 1 yr prior to malignancy, n (%)	16 (76)
Anemia, HB < 110	14
Leukopenia, WBC < 3.0	10
Thrombocytopenia, TPC < 130	8
Cytopenia leading to discontinuation or decreased DMARD	12
BVAS at GPA diagnosis, median (range)	21 (11–36)[1]
VDI at time of hematological malignancy, median (range)	5 (1–10)[1]

[1] Range min–max. [2] C-ANCA/PR3-ANCA unknown in the 5 patients diagnosed before ANCA testing was available (1968–1982). GPA: granulomatosis with polyangiitis; ANCA: antineutrophil cytoplasmic antibody; c-ANCA: cytoplasmic ANCA; PR3-ANCA: proteinase-3 ANCA; P-ANCA: perinuclear ANCA; MPO-ANCA: myeloperoxidase ANCA; HB: hemoglobin; WBC: white blood cells; TPC: total platelet count; DMARD: disease-modifying antirheumatic drugs; BVAS: Birmingham Vasculitis Activity Score; VDI: Vasculitis Damage Index.

Median VDI at the time of leukemia diagnosis was 5 (range 1–10).

Cytopenia (regardless of lineage) was seen in 16 cases (76%), all during treatment with an immunosuppressive drug. In total, 14 of the patients had at least 1 episode of anemia, 10 had leukopenia, and 8 had thrombocytopenia. All combinations of cytopenia were observed, anemia being the most common (n = 14). Six patients had pancytopenia, and all 6 later developed AML or myelodysplastic syndrome (MDS)-AML. In 12 cases, the cytopenia resulted in tapering or discontinuation of disease-modifying antirheumatic drug (DMARD) treatment.

One patient underwent surgery for a cancer of the prostate 6 years before the hematological diagnosis; no other malignancies were registered before the hematological malignancy.

GPA treatment. All the 21 GPA cases with hematological malignancy had been treated with systemic CS for their GPA and 15 of them had received continuous CS treatment throughout the GPA course (70%; Table 2). Median duration of CS treatment was 80 months (range 9–240).

All 21 patients had also been treated with CYC. In the majority of the cases, CYC was given as initial remission-inducing therapy in combination with steroids. The median duration of CYC treatment was 57 months (range 6–228) and the median cumulative dose was 96.5 g (range 9–233). Only 2 patients had received < 25 g cumulative CYC. Maximum daily doses of CYC ranged from 100–400 mg. The doses were generally tapered and minimum daily doses were 25–125 mg. In general, the treatment duration of CYC was longer and the cumulative absolute dose higher in the male than in the female patients (Table 2). The reasons for the discontinuation of CYC were in most cases stable disease, and in 1 case cytopenia.

Other DMARD given as maintenance therapy were methotrexate, azathioprine, mycophenolate mofetil, and cyclosporine. Five patients had not been treated with any other immunosuppressant than alkylating agents (CYC and/or chlorambucil) and steroids.

Characteristics and treatment of hematological malignancy. The median time from GPA diagnosis to hematological malignancy was 8 years (5–21; Table 3). The majority of the 21 cases had been diagnosed with hematological malignancy in 1990 or later (n = 17, 81%). All the leukemia were of myeloid origin (Table 3). Sixteen of the patients had AML (76%, 12 men and 4 women) and of these, 9 had a preceding myelodysplastic syndrome (MDS-AML). Another 3 cases had MDS without signs of development into AML and 2 cases had chronic myeloid leukemia (CML). Cytogenetic analysis had been performed in 9 cases of AML or MDS-AML, as well as in both cases of CML. The most frequent cytogenetic aberration was partial or entire lack of chromosome 7, which was observed in 6 of the AML/MDS-AML cases. In 1 case of MDS-AML, cytogenetic analysis was normal, and in 1, the cytogenetic analysis showed trisomy 13. One MDS-AML case had 3 deletions: chromosome 7, 5, and 17. One CML case was positive for the Philadelphia chromosome [t(9;22)(q34;q11)].

Among the patients with AML and MDS-AML, 6 patients were given standard induction chemotherapy, 1 was given noncytotoxic experimental therapy, and 1 was also given consolidation chemotherapy. One patient with CML was treated with hydroxyurea and 1 with imatinib, the latter being the only patient alive and in remission at end of followup. However, this patient had several relapses of GPA. None of the MDS cases was treated with chemotherapy.

Persisting GPA activity was observed in 1 case after AML diagnosis and despite chemotherapy for the AML. In 2 cases,

Table 2. GPA treatment in patients developing hematological malignancy. Values are n (%) or median (range) unless otherwise specified.

Cases, n = 21	Total
Systemic steroids	21 (100)
Continuous steroid treatment	15 (70)
Median duration systemic steroids, mos	80 (9–240)[1]
CYC	21 (100)
Median duration CYC, mos	57 (6–228)[1]
Median cumulative dose CYC, g	96.5 (9–233)[1]
Median duration CYC, men, mos	59 (28–228)[1]
Median duration CYC, women, mos	16 (6–92)[1]
Median cumulative dose CYC, men, g	100 (64–233)[1]
Median cumulative dose CYC, women, g	60 (15–233)[1]
Azathioprine, n	14
Methotrexate, n	7
Cyclosporine, n	3
Chlorambucil, n	3
Median duration chlorambucil, mos	22 (8–32)[1]
Mycophenolate mofetil, n	1

[1] Range min–max. GPA: granulomatosis with polyangiitis; CYC: cyclophosphamide.

Table 3. Type of hematological malignancy, time from GPA diagnosis, and survival time.

Type	Total, n = 21	Median Time from GPA Diagnosis, Yrs (range min–max)	Median Survival Time, Mos (range min–max)
All cases	21	8 (5–21)	7.5 (0.25–117)*
MDS	3	16 (6–21)	12 (2–12)
MDS developing to AML	9	6 (5–14)	7.5 (2–23)
AML	7	8 (5–19)	4 (0.25–12)
CML	2	13 (11–15)	62.5 (8–117)*

* At end of followup December 31, 2012. GPA: granulomatosis with polyangiitis; MDS: myelodysplastic syndrome; AML: acute myeloid leukemia; CML: chronic myeloid leukemia.

there was a relapse of activity in GPA after diagnosis of MDS (untreated) and CML (treated), respectively.

Survival. Twenty of the 21 patients died during followup. The causes of death were in 11 cases directly related to the leukemia, and in 5 cases, infections were the immediate cause of death. Other causes of death were heart failure, myocardial infarction, and massive hemorrhages. The median overall survival (OS) from diagnosis of hematological malignancy in the 20 patients who died during followup was 7 months (range 0.25–23). The AML cases had the shortest survival with a median OS of 4 months (0.25–12), followed by the patients with MDS-AML with a median OS of 7.5 months (2–23) from the diagnosis of the MDS.

DISCUSSION

In our large study of patients with a verified diagnosis of GPA and hematological malignancy, based on prospectively collected population-based data, we identified 21 patients with GPA and hematological malignancy other than lymphoma. All the 21 cases had myeloid malignancies (myeloid leukemia or MDS).

Though the increased risk of hematopoietic cancers in GPA has previously been noted[6,7], our study adds further detailed knowledge about the relation between GPA and hematological malignancy. First, the patients with GPA in our study all had a severe generalized disease with widespread organ involvement. The fact that VDI, reflecting disease damage over time, was as high as 5 at diagnosis of hematological malignancy indicates that the inflammatory disease had not been easy to manage and that remission had not been permanently achieved in all cases. It has previously been reported that BVAS > 8 at diagnosis and VDI > 4 at 6 months predicted significantly higher mortality[21,28].

Second, the patients had all been treated with CYC in high doses over a prolonged period of time. This may reflect treatment traditions of the time, but might also be a consequence of the severity of the GPA disease.

Although cytogenetic analysis was not performed in all cases, deletion of chromosome 7 was noted in several patients and also deletion of 5 and 17 (in 1 patient). These aberrations have previously been associated with hematological malignancy occurring in patients treated with alkylating agents, and have been associated with a poor prognosis[29,30]. The hematological malignancy occurred after a median latency of 8 years after the diagnosis of GPA. This is also in line with findings in other cancers developing after treatment with alkylating agents[7,8].

Altogether, an association with treatment and development of malignancy in these patients seems plausible. No "safe" dose of CYC has been identified, and doses above the relatively modest cumulative doses of 25–36 g have been associated with increased risk of bladder cancer[7,8].

The disease burden as a risk factor for malignancy is difficult to separate from the effects of treatment in these patients. Recent progress in the management of GPA, including rituximab as an induction and maintenance therapy, denotes a possibility of reducing the use and dosage of CYC[31,32]. However, CYC in combination with CS is still used in a majority of patients with GPA[33]. Longterm followup of these patients will show whether this change in therapy decreases cancer incidence.

Cytopenia related to treatment is a well-known side effect, and leukopenia as well as anemia, thrombocytopenia, and neutropenia occur in more than 1/100 patients treated with CYC. In our study, about 70% of the patients experienced any cytopenia. It is not clear whether this reflects the effect of the total burden of immunosuppression or indicates an increased susceptibility to bone marrow toxicity. If an increased sensitivity of the bone marrow is present, cytopenia during CYC treatment could be a warning sign for a subsequent MDS or leukemia development. Also, a period of cytopenia often precedes the development of MDS in patients not previously exposed to CYC[22].

Survival after the diagnosis of hematological malignancy in these patients was poor. The median survival time for the AML cases was only 4 months compared to the median survival of 9 months for patients followed in the Swedish Acute Leukemia registry[34]. Prognostic factors in AML in general include age, performance status, and pretreatment cytogenetic profile. Median age at AML diagnosis according to the Swedish Acute Leukemia registry is 72 years, with a peak incidence at 80–85 years. A majority of our patients were above 70 years at the date of malignancy and tended to have a nonfavorable cytogenetic profile. Regardless of response to treatment, leukemia is associated with bone marrow failure and increased susceptibility to infections, the latter being the most common direct cause of death[35]. In our present study, the hematological malignancy in itself was more often the immediate cause of death. It must be kept in mind that the treatment options for hematological malignancies have changed during the study period and direct comparison of survival with more recently diagnosed cases is therefore not possible.

The strengths of our present study include the population-based setting, the verification of both the GPA and hematological malignancy in all the cases, and the detailed information on treatments including cumulative CYC dose for all patients. Although register coverage for malignant disease is almost 100% in the cancer register, early cases of MDS were not consequently recognized and classified as MDS before 1990 and could have been missed.

Our study emphasizes the longterm risk of leukemia and MDS in CYC-treated, severely ill patients with GPA. Knowledge of an association between high cumulative CYC dose, not only with bladder cancer, but also with myeloid hematological malignancies, is essential. Cytopenia during the course of GPA may be a warning sign and warrants a liberal attitude toward bone marrow examination.

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