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ORIGINAL ARTICLE

Concomitant association of giant cell arteritis and malignancy: a multicenter retrospective case-control study

S. Deshayes[1] · E. Liozon[2] · N. Chanson[3] · K. Sacré[3] · T. Moulinet[4] · C. Blanchard-Delaunay[5] · O. Espitia[6] · M. Groh[7] · M. Versini[8] · T. Le Gallou[9] · J.-E. Kahn[10] · V. Grobost[11] · S. Humbert[12] · M. Samson[13] · R. Mourot Cottet[14] · K. Mazodier[15] · A. Dartevel[16] · J. Campagne[17] · A. Dumont[1] · B. Bienvenu[18] · M. Lambert[19] · A. Daumas[20] · D. Saadoun[21] · A. Aouba[1] · H. de Boysson[1] · on behalf of the French Study Group for Large Vessel Vasculitis (GEFA)

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Abstract

Introduction Some studies suggest that there is an increased risk of malignancies in giant cell arteritis (GCA). We aimed to describe the clinical characteristics and outcomes of GCA patients with concomitant malignancy and compare them to a GCA control group.

Method Patients with a diagnosis of GCA and malignancy and with a maximal delay of 12 months between both diagnoses were retrospectively included in this study and compared to a control group of age-matched (3:1) patients from a multicenter cohort of GCA patients.

Results Forty-nine observations were collected (median age 76 years). Malignancies comprised 33 (67%) solid neoplasms and 16 (33%) clonal hematologic disorders. No over-representation of a particular type of malignancy was observed. Diagnosis of GCA and malignancy was synchronous in 7 (14%) patients, while malignancy succeeded GCA in 29 (59%) patients. Malignancy was fortuitously diagnosed based on abnormalities observed in laboratory tests in 26 patients, based on imaging in 14 patients, and based on symptoms or clinical examination in the nine remaining patients. Two patients had a concomitant relapse of both conditions. When compared to the control group, patients with concomitant GCA and malignancy were more frequently male ($p < 0.001$), with an altered general state ($p < 0.001$), and polymyalgia rheumatica ($p < 0.01$).

✉ H. de Boysson
deboysson-h@chu-caen.fr

[1] Department of Internal Medicine and Clinical Immunology, Normandie Univ, UNICAEN, CHU de Caen Normandie, Avenue de la Côte de Nacre, 14000 Caen, France

[2] Department of Internal Medicine, CHU Limoges, Limoges, France

[3] Department of Internal Medicine, Hôpital Bichat, Paris, France

[4] Department of Internal Medicine, Hôpitaux Privés de Metz, Metz, France

[5] Department of Internal Medicine, Centre Hospitalier Georges Renon, Niort, France

[6] Department of Internal Medicine, CHU Nantes, Nantes, France

[7] Department of Internal Medicine, National Referral Center for Hypereosinophilic Syndromes (CEREO), Hôpital Foch, Suresnes, France

[8] Institut Arnault Tzanck, Saint Laurent du Var, France

[9] Department of Internal Medicine, CHU Rennes, Rennes, France

[10] Department of Internal Medicine, Hôpital Ambroise Paré, Boulogne Billancourt, France

[11] Department of Internal Medicine, CHU Estaing, Clermont-Ferrand, France

[12] Department of Internal Medicine, CHU de Besançon, Besançon, France

[13] Department of Internal Medicine and Clinical Immunology, CHU Dijon, Dijon, France

[14] Department of Internal Medicine, Hôpital Civil, Strasbourg, France

[15] Department of Internal Medicine, Hôpital de la Conception, Marseille, France

[16] Department of Internal Medicine, CHU Grenoble, Grenoble, France

[17] Department of Infectious and Systemic Diseases, Hôpital d'Instruction des Armées, Metz, France

[18] Department of Internal Medicine, Hôpital Saint Joseph, Marseille, France

[19] Department of Internal Medicine, CHU de Lille, Lille, France

[20] Department of Geriatric and Internal Medicine, CHU de Marseille, Marseille, France

[21] Department of Internal Medicine, Hôpital Pitié Salpétrière, Paris, France

Conclusions This study does not indicate an over-representation of any particular type of malignancy in GCA patients. Initial follow-up dictated by vasculitis may have led to an early identification of malignancy. Nevertheless, GCA male patients with an altered general state and polymyalgia rheumatica might more frequently show concomitant malignancies.

Keywords Giant cell arteritis · Hematologic neoplasms · Malignancy · Neoplasms

Introduction

Giant cell arteritis (GCA) is a large-vessel vasculitis affecting 1–113/100,000 patients ≥ 50 years old; most frequently, women are affected (a sex ratio of 2.3). This condition is associated with polymyalgia rheumatica (PMR) in approximately 40% of the cases [1, 2]. To date, the triggering factor of GCA remains unknown [3].

Some auto-immune conditions have been shown to be associated with an increased risk of acute myeloid leukemia, myelodysplastic syndromes, and myeloproliferative neoplasms (odds ratios of between 1.2 and 2) [4, 5]. Specifically, several auto-immune diseases might be associated more frequently with malignancies, such as connective tissue disorders, especially dermatomyositis and Sjögren's syndrome, but also vasculitis, including cutaneous leukocytoclastic vasculitis, polyarteritis nodosa, and immunoglobulin A vasculitis [6–11]. Indeed, the prevalence of malignancies among patients with vasculitis is estimated at between 2 and 10%, and patients with vasculitis have an increased risk (odds ratio 3.7) of developing cancer in the 2 years preceding or following its onset [8–12]. A significant standardized incidence ratio (SIR) of overall cancer was observed in patients with vasculitis excluding Kawasaki disease (SIR = 1.75), especially in the first year (SIR = 2.86) [13].

Conversely, malignancies can be complicated by vasculitis, especially malignant blood diseases such as hairy cell leukemia and myelodysplastic syndromes, and, less frequently, solid tumors, mainly pulmonary, genitourinary, and gastrointestinal cancers [6, 9, 10, 14]. Specifically, the frequency of vasculitis in hematological malignancies is approximately 7–23% in myelodysplastic syndromes and 2–4% in lymphoid malignancies [15–22].

Studies analyzing the association between GCA and malignancies are scarce and show paradoxical results. Some retrospective studies indicate an association between both conditions in 10 to 25% of GCA patients [23–27]. GCA has also been found to be associated with an increased risk of myeloproliferative neoplasms (odds ratio 5.9) [5]. However, when compared to a control group, the malignancy frequency or mortality is not increased [26–30]. Some prospective studies indicated an association between GCA and malignancy in 6.5 to 16% of their patients [31–35], but other do not [32, 36]. A meta-analysis combining both GCA and PMR found a significant pooled risk-ratio of 1.14, which is higher during the first 6 months after GCA diagnosis (pooled risk-ratio 2.16) [37]. A recent meta-analysis including 1972 GCA patients did not find an increased standardized mortality ratio due to cancer (SMR 0.833, $p = 0.243$) [30].

In this study, we aimed to determine which types of malignancies are associated with GCA and analyzed their concomitant outcomes. We compared these patients to a control group without malignancy to determine whether GCA patients with concomitant malignancy exhibit specific findings at onset.

Materials and methods

Study design and patients

The patients were selected through an e-mail sent to physicians belonging to the French Internal Medicine Society (SNFMI) and the French Study Group for Large Vessel Vasculitis (GEFA). Patients had to satisfy the two following criteria to be enrolled in the study. First, the diagnosis of GCA was based on the fulfilling of at least 3 criteria of the American College of Rheumatology for GCA [38] or was based on the satisfaction of 2 criteria associated with the demonstration of large-vessel involvement on imaging. Second, patients had to be diagnosed with histologically proven solid neoplasm or clonal hematologic disorder within 1 year before or after the diagnosis of vasculitis. We also enrolled patients who relapsed from a malignancy during the year preceding or following the GCA diagnosis. Physicians who enrolled patient(s) received a standard data collection form. Previously published patients were not included. A random group of age-matched (3:1) control patients from a multicenter cohort of GCA patients from Caen, Limoges, Dijon, Paris, Lille, and Marseille University Hospitals was constituted. Patients were paired on age but not on sex because of the frequency differences regarding malignancies between men and women.

This study was conducted in compliance with good clinical practices and the Declaration of Helsinki principles. In accordance with French public health law (Art. L 1121–1-1, Art. L 1121–1-2), formal approval from an ethics committee is not required for this type of study. The manuscript was prepared in accordance with STROBE guidelines.

Parameters studied and definition

For each patient, detailed information regarding GCA and malignancy was recorded. Demographics, past medical history, clinical presentation, date of onset, treatment, and outcomes (including relapse and death) for both conditions were noted. Regarding vasculitis, clinical manifestations, laboratory tests, and radiological and histological findings were collected when available.

Alteration of the general state was defined as a combination of fatigue and a weight loss of > 10%.

Relapse of GCA was defined as the recurrence of clinical symptoms or an increase of acute phase reactants requiring an increase of GCA-related treatments without any other identified causes.

Statistical analysis

Categorical variables are reported as percentages and were compared using Chi^2 or Fisher's tests according to expected frequencies. Continuous variables are expressed as medians [quartile 1–quartile 3] and were analyzed using the nonparametric Mann–Whitney test. Association between survival and the presence of malignancy was evaluated by the log-rank test. A p value < 0.05 was considered significant. All tests were performed using GraphPad Prism 7 (GraphPad Software Inc., San Diego, CA).

Results

Forty-nine patients were included (20 (41%) women with a median age at GCA diagnosis of 76 [69–79] years; see Table 1). Patients had a median follow-up of 26 [8–57] months. Two (4%) patients were active smokers, and 13 (27%) were ex-smokers; 2 (4%) patients were exposed to asbestos (construction site workers), 6 (12%) patients had a family history of malignancy, and 8 (16%) patients had a previous history of malignancy (4 genitourinary, 2 breast, 2 digestive, 1 lung, and 1 skin carcinomas) that occurred 38 [13–116] months before GCA diagnosis, including 2 patients with a previous history of 2 separate solid tumors. Two patients were still under hormone therapy for a previous prostate cancer, and the other patients were cured of their previous malignancy at the time of GCA diagnosis.

All but two patients fulfilled ≥ 3/5 ACR criteria. The two patients with 2/5 ACR criteria had large-vessel involvement as seen on imaging. Temporal artery biopsy was performed in 47 (96%) patients and was positive in 32 (65%). One patient was initially treated with the combination of glucocorticoids and methotrexate as a steroid-sparing treatment because of a pre-existing psychiatric history. All other patients were treated with glucocorticoids exclusively, with a median initial dose at 0.73 [0.68–0.95] mg/kg/day (52.5 [45–60] mg/day).

Table 1 Characteristics of 49 patients with giant cell arteritis and concomitant diagnosis of malignancy and 147 age-matched control patients

	Concomitant GCA and malignancy (n = 49)	Control group (n = 147)	p value
Demographics			
Age at giant cell arteritis diagnosis	76 [69–79]	76 [69–79]	1
Women	20 (41)	107 (73)	< 0.001
Smokers	13 (27)	25 (17)	0.15
Vasculitis characteristics			
Headaches	36 (73)	112 (76)	0.71
Scalp tenderness	18 (37)	61 (41)	0.56
Jaw claudication	25 (51)	52 (35)	0.06
Ophthalmic troubles	15 (31)	49 (33)	0.73
Abnormalities on temporal artery	18 (37)	52 (35)	0.87
Polymyalgia rheumatica	27 (55)	50 (34)	< 0.01
Large-vessel murmur	6 (12)	19 (13)	0.91
Alteration of the general state	38 (76)	70 (48)	< 0.001
Fever > 38 °C	11 (22)	43 (29)	0.36
Positive temporal artery biopsy	32 (65)	105 (71)	0.42
Relapse	17 (35)	69 (47)	0.14
Number of relapses per patient	0 [0–1]	0 [0–1]	0.36
Death	8 (16)	26 (18)	0.83
Follow-up (months)	26 [8–57]	46 [20–81.5]	0.03

Unless indicated otherwise, values are displayed as absolute number (%) or as median [quartile 1–quartile 3]; *GCA* giant cell arteritis

The types of malignancies that occurred in the 49 patients are listed in Table 2. Solid neoplasms occurred in 33 (67%) patients and were mainly gastrointestinal (n = 9), pleuropulmonary (n = 7), genitourinary tract (n = 7), and breast (n = 6) cancers. Clonal hematologic disorders occurred in the 16 (33%) other patients, including 8 cases of lymphoid blood diseases and 8 myeloid neoplasms. Regarding the 8 patients with a previous history of malignancy, 4 had a relapse of their malignancy within 1 year before or after the diagnosis of vasculitis (2 breast, 1 lung and 1 renal cancers). The two patients still under hormone therapy for a previous prostate cancer had another solid tumor: 1 renal cancer and 1 lung cancer.

Diagnosis of GCA and malignancy was synchronous in 7 (14%) patients; malignancy preceded GCA in 13 (27%) patients with a median delay of 5 [3–8] months; and malignancy followed GCA in 29 (59%) patients with a median delay of 4 [1–8] months. Four (8%) neoplasms were symptomatic (hematuria, hemoptysis, jaundice or bone pain) before (n = 1) or

Table 2 Description of 49 concomitant malignancies encountered in GCA patients

Solid tumors	33 (67%)
Digestive tract*	9 (18%)
Pleuro-pulmonary+	7 (14%)
Genitourinary tract#	7 (14%)
Breast	6 (12%)
Skin°	3 (6%)
Thyroid	1 (2%)
Clonal hematologic disorders	16 (33%)
Lymphoid blood diseases	8 (16%)
Chronic lymphoid leukemia	5 (10%)
Mucosa-associated lymphoid tissue lymphoma	1 (2%)
Myeloma	1 (2%)
Waldenström's macroglobulinemia	1 (2%)
Myeloid neoplasms	8 (16%)
Essential thrombocythemia	4 (8%)
Myelodysplastic syndrome	3 (6%)
Chronic myelomonocytic leukemia	1 (2%)

* Gastrointestinal, pancreatic, and liver cancers ($n = 6$, 2, and 1, respectively)

+ Lung and pleural cancers ($n = 6$ and 1, respectively)

Prostate, bladder, and kidney cancers ($n = 5$, 1, and 1, respectively)

°Melanoma, Kaposi's sarcoma, Merkel cell carcinoma ($n = 1$ each)

after ($n = 3$) GCA diagnosis. Diagnosis of malignancy in other patients was made during a follow-up visit in 5 (10%) patients (3 skin cancers and 2 breast cancers), based on laboratory tests in 26 cases (53%; thrombocytosis, anemia, monoclonal gammapathy, lymphocytosis, or increased prostate specific antigen) and based on imaging in 14 cases (29%; based on positron-emission tomography in 6 cases, based on CT-scan in 6 cases and based on mammography in 2 cases).

Treatments of malignancies included oral, local, and/or intravenous chemotherapy alone in 14 (29%) patients, surgery alone in 8 (16%) patients, surgery and radiotherapy and/or chemotherapy in 9 (18%) patients, radiotherapy and chemotherapy in 2 (4%) patients, radiotherapy alone in 2 (4%) patients, and decrease of corticosteroids in 1 patient who suffered from Kaposi's sarcoma. Twelve (24%) patients did not receive a specific treatment for their malignancy, either because simple monitoring was required (4 chronic lymphoid leukemias, 1 prostate cancer under hormonotherapy, 1 mucosa-associated lymphoid tissue lymphoma and 1 myelodysplastic syndrome) or because the general state of the patient did not allow polychemotherapy (1 myeloma, 2 metastatic pancreas adenocarcinomas, 1 lung cancer and 1 renal cancer, both metastatic). Seven relapses of malignancy were observed in 5 (10%) patients, while GCA was concomitantly in relapse in 2 patients, in remission in 2 patients and cured in 1 patient.

At the end of follow-up, 30 GCA relapses were noted in 17 (35%) patients. Except for the 2 patients with concomitant relapse of both diseases, all relapsing GCA patients had a malignancy that was considered stable or in remission at the time of relapse. Fifteen (21%) patients were weaned from steroids, and the median dose of steroids at last follow-up visit was 6.5 [5–15] mg/day.

Two patients required the adjunction of cyclophosphamide (because of a suspicion of intra-cerebral vasculitis in one case and for a relapsing disease in another) followed by maintenance therapy, either by methotrexate or azathioprine, and 3 other patients needed the adjunction of methotrexate as a steroid-sparing agent. At last follow-up, 9 (18%) patients remained under chemotherapy (3 pleuro-pulmonary, 3 breast, and 1 prostate cancers and 2 essential thrombocythemias), 24 (49%) patients were considered in remission for their malignancy, and 7 (14%) patients remained under simple monitoring. Eight (16%) patients died; 4 died from infectious complications, 3 from a cancer progression and 1 from complications that were secondary to dementia. One patient was lost to follow-up.

By comparison to 147 age-matched controls, patients diagnosed concomitantly with GCA and malignancy were more frequently male ($p < 0.001$), more frequently had an altered general state ($p < 0.001$) and polymyalgia rheumatica ($p < 0.01$) (Table 1). We did not observe an excess of mortality in GCA patients with concomitant malignancy ($p = 0.6$, data not shown). Patients were followed for a longer period in the control group ($p = 0.03$).

Discussion

Our study of patients with concomitant GCA and malignancy showed an over-representation of males, alteration of the general state, and PMR when compared to the control group. This real-life analysis did not find any over-representation of any particular type of cancer in GCA patients. To our knowledge, only two studies determined the frequency and type of malignancies concurrent with GCA that were diagnosed less than 1 year before or after symptoms appeared. Liozon et al. analyzed the data from 20 patients (7.4%) with both diagnoses in their GCA cohort and reviewed 27 similar published reports. Solid tumors were mainly represented by gastrointestinal tract cancer, and malignant blood diseases were mainly represented by myelodysplastic syndromes and lymphoid disorders. GCA patients with concurrent malignancy had more rheumatic involvement, as in our cohort [24]. In their recent prospective study, Ješe et al. reported that 7/107 (6.5%) of GCA patients had a diagnosis of malignancy within 1 year before or after the diagnosis of vasculitis. The SIR was 4.61 (95% CI, 2–9.26) [35]. The increased frequency of males seen in our study may reflect, at least in part, the higher SIR of neoplasms in males

when compared to females (353.2/100,000 and 284.5/100,000 person-years in France in 2017, respectively [39]). The higher frequency of alteration of the general state in our patients with concomitant malignancy might be secondary to the underlying neoplasm, but we cannot exclude a recall bias.

The malignancies encountered were heterogeneous, thereby excluding a single causing tumor antigen. Very few patients ran a paraneoplastic course, with only 4% of our patients relapsing concomitantly from malignancy and GCA. Nevertheless, malignancy might serve as a trigger and, once triggered, vasculitis might run a course that is independent of the malignancy [40]. This association might also be fortuitous because both diseases occur in the elderly. Indeed, the median age at malignancy diagnosis in France is 67–68 years [39]. Another likely explanation is follow-up bias, which might account for the higher risk of cancer in the first year after GCA diagnosis [34, 37]. Indeed, these patients are more likely to undergo clinical, biological, and radiological examinations, and malignancies have been diagnosed in more than 50% of the cases after GCA diagnosis in our patients. This lead time bias might explain in part the significantly lower risk of death due to cancer observed in the GCA patients compared to the controls within 10 years after GCA diagnosis in a Danish study [41] or the standardized mortality odds ratios at 0.52 for deaths related to solid neoplasms in a recent French study [42], while recalling that cancer represents the third-leading cause of deaths in GCA [29].

Near one third of patients had a fortuitous malignancy diagnosis that was established based on imaging. Patients with GCA are frequently subjected to imaging to test for large-vessel involvement. Whole-body imaging techniques, such as PET/CT or CT scanning, are sensitive tools to demonstrate large-vessel involvement and can help in diagnosing malignancy in some patients. Although we cannot encourage whole-body imaging for malignancy screening in all GCA patients, our study suggests that male patients with altered general state and PMR might first be targeted.

Although we did not identify a strong association between GCA and malignancy, several pathophysiological hypotheses have been formulated regarding the association between malignancy and vasculitis: malignant degeneration of tissues undergoing chronic immune stimulation; subclinical infections or aberrant antibody production due to neo-antigen exposure; increased blood viscosity resulting from malignant neoplasms; increased production of pro-inflammatory cytokines by malignant tumor cells; tumors may invade vascular endothelium; monoclonal immunoglobulin activity, including cryoglobulin deposits; a common pathway between autoimmune diseases and malignancy, such as an impairment of immunosurveillance or mutations in genes that are responsible for repair and apoptosis, which are implicated in both conditions; or the onset of several alterations in the innate and adaptive immune systems in malignant blood diseases [7–9, 17, 22, 43–45]. The absence of a parallel evolution between GCA and malignancy found in our patients might be due to the retrospective nature of this study, the limited follow-up or the patient selection. Prospective large-scale studies are needed to determine whether a link exists between these two conditions.

Conclusion

This study did not indicate an over-representation of any particular type of malignancy within a selected population of GCA patients from tertiary centers, and we did not find direct links between GCA and malignancy; however, prospective large-scale studies are required to confirm these results. Our study shows an over-representation of male gender, alteration of the general state and polymyalgia rheumatica in GCA with concomitant malignancy. Initial clinical, and paraclinical follow-up dictated by vasculitis might have led to an early identification of associated malignancy and might thus represent a lead time bias. Nevertheless, a thorough clinical and biological examination and the use of whole-body imaging (frequently asked for in GCA to determine if large-vessel involvement is present) may help in diagnosing malignancy. In the absence of recommendations, male patients with an alteration of the general state and polymyalgia rheumatica should probably be examined for malignancy first.

Compliance with ethical standards

Ethical standards This study was conducted in compliance with good clinical practices and the Declaration of Helsinki principles. At the time of this study, in accordance with French public health law (Art. L 1121-1-1, Art. L 1121-1-2), formal approval from an ethics committee was not required for this type of observational study. Our local ethics committee confirmed the observational non-interventional retrospective nature of our cohort.

Conflicts of interest This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Maxime Samson declares invitations to congresses by Abbvie, Roche Chugaï, Actelion, Novartis and LFB; symposium for Roche Chugaï and belongs to scientific committee of Roche Chugaï. The other authors declare that they have no relevant financial interests.

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