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Original article

Antineutrophilic cytoplasmic antibody-associated vasculitis and malignant hemopathies, a retrospective study of 16 cases

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ABSTRACT

Objectives: ANCA-associated vasculitis are severe autoimmune pathologies that are characterized by inflammation and necrosis of the small vessels. The physiopathological mechanisms are complex and have yet to be totally elucidated. Several environmental factors have been described as being associated: medications, infectious agents. . . and rarely, neoplasms.
Methods: We performed a retrospective multicenter study over a period of 12 years with a view to describing the association of ANCA-associated vasculitis and malignant hemopathies, excluding hemopathies secondary to vasculitis treatment.
Results: Sixteen patients with ANCA-associated vasculitis with an hemopathy were identified. The gender ratio was 7 and the mean age was 65 years. The frequency of this association is estimated at 1%. The ANCA-associated vasculitis were micropolyangiitis ($n = 7$), followed by granulomatous polyangiitis ($n = 4$), vasculitis limited to the kidney ($n = 3$), and eosinophilic granulomatous polyangiitis ($n = 2$). The associated malignant hemopathies were mainly non-Hodgkin's lymphoma in seven cases and myelodysplasia in five cases. The other hemopathies were: Hodgkin's disease, hypereosinophilic syndrome, and Waldenström's macroglobulinemia. Hemopathy treatment was associated with vasculitis treatment in seven cases.
Conclusion: The association of ANCA-associated vasculitis and malignant hemopathy is rare but must nevertheless be recognized because: (i) the clinical signs of both pathologies are not specific, (ii) the survival scores that are used for ANCA-associated vasculitis do not appear to be applicable, (iii) both pathologies must be taken into account in order to implement an effective therapeutic strategy that limits the inherent risks.

1. Introduction

Antineutrophilic cytoplasmic antibodies (ANCA)-associated vasculitis are severe autoimmune pathologies that are characterized by inflammation and necrosis of the small vessels. Granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis) (GPA), micropolyangiitis (MPA), eosinophilic granulomatous polyangiitis (formerly known as Churg-Strauss syndrome) (EGP), and ANCA vasculitides limited to the kidney can be distinguished [1,2]. Classically, in patients with GPA, ANCA recognize proteinase 3 (PR3) whereas in MPA and EGP, myeloperoxydase (MPO) is the principal antigen. The prognosis for ANCA-associated vasculitis is severe with a 5-year mortality rate that is evaluated at 25%. The relative risk of death is therefore 2.6 compared with a population paired for age and gender [3].

The physiopathological mechanisms are complex and have yet to be fully elucidated. Several environmental factors have been described as being associated with the development of ANCA-associated vasculitis: medications (propylthiouracil [4]), silica [5], as well as certain infectious agents (*Staphylococcus aureus*). More rarely, ANCA-associated vasculitis have been described within the context of neoplasms [6,7]. Isolated cases of ANCA-associated vasculitis with hemopathies have been described in the literature [6–8]. However, no study has provided an estimation of the incidence of this association or its treatment.

The aim of this study was to describe the association of ANCA vasculitides and malignant hemopathies in order to know (i) its frequency, (ii) the malignant hemopathies involved, (iii) their clinical

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characteristics, and (iv) the evolution under treatment of these two entities.

2. Methods

In a retrospective multicenter study, we identified by local database all patients with ANCA-associated vasculitis diagnosed during the period from 2000 to 2012 in two centres [University Hospital of Clermont-Ferrand (departments of nephrology, internal medicine and hematology, and to the University Hospital of Tenon, department of nephrology)]. All patients 18 and over with a malignant hemopathy and concomitant ANCA-associated vasculitis, defined in this study as both pathologies being diagnosed in less than a two-year interval, were included in the study. Exclusion criteria were the incomplete collection of data and patients with malignant hemopathy considered as secondary to ANCA-associated vasculitis's treatment. We also included patients who corresponded to inclusion criteria from the database of the French Vasculitis Study Group prior to 2012.

Data were collected from medical files, hospital records, and the French Vasculitis Study Group database. This is a database that includes the clinical, sociodemographic and therapeutic characteristics of all cases of vasculitides reported to this French reference group since its creation in 1983. The data collected included the sociodemographic characteristics of the patients, the type of ANCA-associated vasculitis, the type of hemopathy, the diagnosis dates of these pathologies, the clinico-biologic characteristics of these pathologies, their prognostic scores, the therapies performed, and patient outcomes up to the last follow-up. The Birmingham Vasculitis Activity Scores (BVAS) and the Five-Factor Scores (FFS) were calculated for each patient [9,10]. FFS were calculated according to the latest French Vasculitis Study Group criteria [9]. One point was assigned for each of the following criteria: the presence of renal involvement, digestive involvement, cardiac involvement, age > 65. One point was withdrawn if there was ENT involvement. The frequency of the two-disease association was made with the proportion of patients with ANCA-associated vasculitis who had a concomitant hemopathy. The ethical committee of the institution approved the extraction of data from the patient charts.

3. Results

We identified 613 patients with ANCA-associated vasculitis in the two medical centres, and 1631 patients in the French Vasculitis Study Group's database. Sixteen patients with a concomitant malignant hemopathy were found. The characteristics of this cohort are provided in Table 1. The gender ratio (male/female) was 7 (14/2) and the mean age was 65 years. The frequency incidence rate of this association was estimated from 3 different registries: the Clermont-Ferrand group (7/457 or 1.6%), the Department of nephrology of the University Hospital of Tenon (3/156 of 1.28%), and the French Vasculitis Study Group (6/1,631 or 0.37%). In the majority of cases, both diagnoses were almost concomitant. The mean period between each diagnosis was 6 months (1–19 months).

3.1. ANCA-associated vasculitis

The ANCA-associated vasculitis was predominantly MPA ($n = 7$), followed by GPA ($n = 4$), vasculitides limited to the kidney ($n = 3$), and EGP ($n = 2$). The classic clinical signs of ANCA-associated vasculitis were present. In most of the cases, there was a change in the general state of health with asthenia, weight loss ($n = 10$). The most frequent organ involvement was renal ($n = 10$). The clinical picture was therefore that of a rapidly progressive glomerulonephritis. Two patients required dialysis. The other pathologies involved were purpura ($n = 6$), intra-alveolar hemorrhage ($n = 5$), arthralgia ($n = 3$), peripheral ($n = 4$) and central ($n = 1$) neuropathy, and more rarely, urogenital ($n = 1$), ophthalmologic ($n = 1$), ENT ($n = 1$), digestive ($n = 1$), and cardiac ($n = 1$). In the majority of cases, ANCA was diagnosed by indirect immunofluorescence tests ($n = 13$). A specificity test by Elisa was performed in 13 out of the 16 patients: 7 had myeloperoxydase specificity, 4 had antiproteinase-3 specificity, and no specificity was detected in 2 patients.

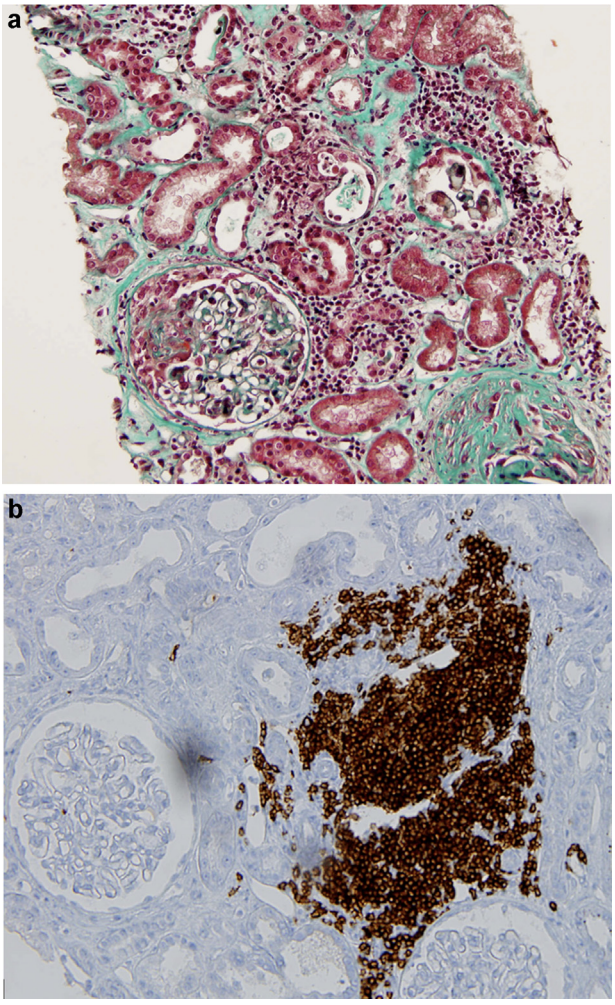

Fig. 1. Histologic results of renal biopsy in patient 1; a: classic optic microscope study (*coloration trichrome de Masson*). Extracapilliary glomerulonephritis with cellular growth in 40% of the glomeruli associated with inflammatory mononuclear infiltrate estimated at 20% of the biopsied surface; b: immuno-histochemical study mononuclear infiltrate. B lymphocyte markers (CD20, CD79a) and CD5+ within the framework of mantle lymphoma.

In 10 vasculitis patients with renal involvement, histologic confirmation was performed by renal biopsy by puncture with optic microscope study and in immunofluorescence. The histology results revealed pauci-immune extracapilliary glomerulonephritis (ECGN) (absence of deposits in immunofluorescence). In 3 samples (30%), a mononuclear infiltrate was found in the interstitium. This infiltrate was classified in all of the cases, ensuring its clonal character. In one of the cases, this immuno-histochemical study diagnosed a hemopathy: large B-cell lymphoma (CD19, CD22 markers) in an isolated renal location. In another case, the infiltrate was an atypical lymphoplasmacytic monomorphic infiltrate and a diagnosis of Waldenström's macroglobulinemia was made following a myelogram. Finally, in the last case, an interstitial infiltrate by CD5+ B lymphocytes (CD20, CD79a markers) was described in a patient with previously diagnosed mantle cell lymphoma (Fig. 1).