Prevalence of rheumatic manifestations and antineutrophil cytoplasmic antibodies in haematological malignancies. A prospective study

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Abstract

Objective. To evaluate the prevalence of antineutrophil cytoplasmic antibodies (ANCA) and rheumatic manifestations associated with chronic haematological malignancies.

Methods. Two groups of patients were prospectively studied (group I: 60 patients with myelodysplastic syndromes and group II: 140 patients with lymphoid malignancies) for clinical ‘immune’ manifestations and ANCA.

Results. In the myelodysplastic group, six patients had ANCA-negative systemic medium-size vasculitis, one had systemic vasculitis with cytoplasmic ANCA, one relapsing polychondritis, one giant cell arteritis, one polymyalgia rheumatica, one polyarthritis and two fasciitis. In group II, two patients had ANCA-negative systemic vasculitis, two had leucocytoclastic vasculitis associated with tuberculosis, two had polyarthritis, one polymyalgia rheumatica and one giant cell arteritis. Six sera were ANCA-positive with perinuclear pattern in four cases, atypical pattern in one and cytoplasmic pattern in one. Two sera had anti-myeloperoxidase (MPO) specificity, and others had no known specificity; none had anti-proteinase 3 (PR3) specificity. Global prevalence of ANCA in our cohort was 3%, similar to the French general population.

Conclusion. Polyarteritis nodosa-type systemic vasculitis and polymyalgia rheumatica were the most frequent findings (18%) in myelodysplastic syndromes and particularly in chronic myelomonocytic leukaemia. ANCA were not helpful for the diagnosis of vasculitis. Vasculitis associated with infection, in particular tuberculosis, must be ruled out.

Key words: Antineutrophil cytoplasmic antibodies, Vasculitis, Rheumatic manifestations, Polymyalgia rheumatica, Lymphoma, Myelodysplasia.
factor (RF), cryoglobulinaemia and complement explorations (CH50, C3, C4).

**ANCA assay**

The test for ANCA was performed by indirect immunofluorescence (IIF) on ethanol-fixed neutrophils as previously described [5]. The positive sera (superior to 1:30) detected by this assay were tested for anti-myeloperoxidase (MPO) and anti-proteinase 3 (PR3) using an antigen-specific enzyme-linked immunosorbent assay (ELISA; Eurodiagnostica, Gentilly, France).

**Results**

In group I (60 MDS), 19 had CMML, 10 RA, 16 RAEB, 10 RAEB-T and five RARS. Ten patients had 5q deletion, one trisomy 8 and one trisomy 21. In group II (140 lymphoid neoplasias), 35 had CLL, 25 WM, 18 MM, 11 HCL and 51 non-Hodgkin's lymphoma (NHL), 26 of low grade and 25 of intermediate or high grade with eight angioimmunoblastic lymphadenopathies.

Six patients, three in each group, had positive ANCA determination by IIF assay (Table 1): four perinuclear pattern with anti-MPO in two, one atypical and one cytoplasmic with no anti-MPO, PR3, elastase, lactoferrin, lysozyme, or bactericidal/permeability-increasing protein (BPI) specificity. No patient had ANA or cryoglobulinaemia. Among the five patients with perinuclear and atypical ANCA, none had immune manifestations and one had neutrophilic dermatitis. The patient with cytoplasmic ANCA fluorescence had CMML associated with systemic vasculitis. The global prevalence of ANCA positivity in our haematological population was 3%, with 5% in group I and 2% in group II. No patient who received IFN-α developed ANCA or rheumatic/vascular manifestations.

Among the 194 ANCA-negative patients, 12 had vasculitis (Table 2). In the group of MDS, six had medium-size vasculitis fulfilling American College of Rheumatology (ACR) criteria for classic polyarteritis nodosa (PAN), one had relapsing polychondritis, one seronegative polyarthritis, one polymyalgia rheumatica (see Table 2 for others). There was no correlation between rheumatic manifestations, haematological neoplasia, ANCA positivity and cytogenetic findings. In group II (Table 2), five patients had primary vasculitis: relapsing polychondritis, PAN, giant cell arteritis, cutaneous vasculitis, systemic vasculitis. Two patients had skin vasculitis associated with tuberculosis. Other patients had polyarthritis and polymyalgia rheumatica. Two patients had active chronic hepatitis B without vasculitis or systemic manifestation.

**Discussion**

MDS and several lymphoid neoplasia are sometimes associated with vasculitis or rheumatic manifestations, e.g. polyarthritis or polymyalgia rheumatica [1, 2, 6–11]. Naschitz et al. [1] proposed several mechanisms: invasion of bone, joint, or muscle by tumour, paraneoplastic syndromes, altered immune surveillance causing both rheumatic and neoplastic diseases, or adverse reactions to therapy. Castro et al. [6] in a retrospective review of 162 MDS patients found 16 patients with rheumatic manifestations. The symptoms were cutaneous vasculitis, lupus-like disease, and neuropathy. Enright and Miller [7] identified 30 (13.6%) patients among 221 MDS patients, who had clinical autoimmune disease with three patterns: acute systemic vasculitis (n = 18), chronic or isolated autoimmunity manifestations (n = 11), classic connective tissue disorders (n = 5). In the literature, systemic vasculitis is rare [12–14]. Recently, some authors have emphasized the high frequency of polymyalgia rheumatica associated with MDS [15, 16].

Our study was the first to investigate in a prospective way, the prevalence of rheumatological manifestations during the course of haematological neoplasia. Surprisingly, we found more systemic vasculitis and systemic manifestations than others [6–14], probably due to a recruitment bias. In our cohort, rheumatic manifestations (polyarthritis, polymyalgia, vasculitis) are more frequent in MDS, particularly in CMML. They occurred in 11 cases out of 60 patients (18%) vs seven of 140 (5%) in the lymphoid neoplasia group. In group I, one patient had relapsing polychondritis, which is often associated with MDS [17] and seven had systemic vasculitis. The vasculitis was systemic, generally ANCA negative and involved large- and medium-sized vessels. They fulfilled ACR criteria for classical PAN and were not associated with hepatitis B or C. No correlation was shown between vasculitis and the activity of the haematological disorder, transfusion frequency, treatments or infectious events. We found no relationship between vasculitis, ANCA or cytogenetic abnormalities. Polymyalgia rheumatica and polyarthritis were noted twice in each group and two patients had fasciitis and MDS (Table 2). All these manifestations occurred during the course of the haematological disorder, were

**Table 1. ANCA-positive patients and clinical correlations**

<table>
<thead>
<tr>
<th>Haematological neoplasia</th>
<th>ANCA fluorescence</th>
<th>ANCA titre and specificity</th>
<th>Clinical manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL</td>
<td>pANCA</td>
<td>30 (anti-MPO 11 U)</td>
<td>None</td>
</tr>
<tr>
<td>Waldenström</td>
<td>pANCA</td>
<td>300 (anti-MPO-)</td>
<td>None</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>pANCA</td>
<td>100 (anti-MPO-)</td>
<td>Fever of unknown origin</td>
</tr>
<tr>
<td>RA</td>
<td>pANCA</td>
<td>100 (anti-MPO 13 U)</td>
<td>Neutrophilic dermatosis</td>
</tr>
<tr>
<td>RAEB</td>
<td>pANCA</td>
<td>30 (anti-MPO-)</td>
<td>None</td>
</tr>
<tr>
<td>CMML</td>
<td>cANCA</td>
<td>300 (anti-PR3-)</td>
<td>Systemic vasculitis</td>
</tr>
</tbody>
</table>
Table 2. Rheumatic manifestations in 200 patients with haematological malignancies

<table>
<thead>
<tr>
<th>Haematological neoplasia (n)</th>
<th>Vasculitis (type and number)</th>
<th>Polymyalgia rheumatica and polyarthritis</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelodysplasia (60)</td>
<td>6 systemic vasculitis (ANCA negative)</td>
<td>1 polymyalgia</td>
<td>2 fascitis</td>
</tr>
<tr>
<td></td>
<td>1 systemic cANCA + vasculitis</td>
<td>1 polyarthritis</td>
<td>2 neutrophil dermatosis</td>
</tr>
<tr>
<td></td>
<td>1 giant cell arteritis</td>
<td></td>
<td>1 adult-onset Still’s disease</td>
</tr>
<tr>
<td></td>
<td>1 relapsing polyarthritis</td>
<td></td>
<td>1 antiphospholipid syndrome</td>
</tr>
<tr>
<td>CLL (35)</td>
<td>1 systemic vasculitis (ANCA negative)</td>
<td>1 polyarthritis</td>
<td>1 bronchitis obliterans</td>
</tr>
<tr>
<td></td>
<td>1 systemic vasculitis</td>
<td></td>
<td>1 angioneurotic oedema</td>
</tr>
<tr>
<td></td>
<td>(ANCA negative)</td>
<td></td>
<td>1 inflammatory pseudotumour</td>
</tr>
<tr>
<td>HCL (11)</td>
<td>1 systemic vasculitis (ANCA negative)</td>
<td>2 polyarthritis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 cutaneous vasculitis with tuberculosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 giant cell arteritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waldenström (25)</td>
<td>1 cutaneous vasculitis with tuberculosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 giant cell arteritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoma (51)</td>
<td>None</td>
<td>1 polymyalgia (AIL)</td>
<td>None</td>
</tr>
<tr>
<td>Myeloma (18)</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

not linked to disease activity, and were generally corticosteroid-sensitive. It is important to investigate for infections, in particular tuberculosis, because two patients had leukocytoclastic vasculitis associated with tuberculosis during the course of lymphoid neoplasia.

Patients with MDS have immunological abnormalities in both cellular and humoral immunity [3, 7, 18]. They have deregulated apoptosis with altered neutrophils and are also susceptible to recurrent infections. Such infections and neutrophil alterations could prime neutrophils and theoretically induce ANCA and endothelial damage [19–21]. In immune manifestations associated with lymphoid malignancies, CD5-positive B cells may play a role, producing autoantibodies and monoclonal immunoglobulins [22]. Billström et al. [23] suggest an involvement of CD5 B lymphoid lineage and cytogenetic abnormalities in the genesis of immune-mediated complications in MDS.

To our knowledge, Savige et al. [24, 25] first investigated ANCA in haematological chronic malignancies. In a study of 25 patients, just one with primitive MDS had pANCA without any known specificity on ELISA [25]. Another patient with myelodysplasia had cutaneous vasculitis with anti-PR3 antibodies [24]. Komatsuda et al. [26] described a patient with anti-MPO crescentic glomerulonephritis and MDS with trisomy 7. In lymphoid malignancies, ANCA are very rarely present, sometimes with false positivity [27, 28].

In our series, we found 5% of the MDS group were ANCA positive and 2% of the lymphoid malignancies. The global prevalence of ANCA positivity was 3%, mostly of perinuclear fluorescence pattern. These data are similar to 0–1.8% ANCA positivity in the French hospitalized population [29]. No relationship was found between ANCA positivity, clinical manifestations of vasculitis and the type of haematological malignancy. We found ANCA in one patient of 46 with a monoclonal component, while Ennulf et al. [30] found ANCA in 12 sera of 125 (9.6%) and concluded a non-specific autoreactivity.

In most cases, vasculitis diagnosis is difficult because of the lack of specific symptoms, complex haematological situations and haemostasis disorders, none of which allow invasive diagnostic procedures, e.g. renal or pulmonary biopsies.

In conclusion, the prevalence of ANCA in chronic haematological neoplasia is very low, similar to the general population. We did not find false positive ANCA with monoclonal gammopathy or hypergglubulinaemia. Rheumatic manifestations seem more frequent in MDS than in lymphoid neoplasia, systemic vasculitis and polymyalgia rheumatica being the principal clinical manifestations. They are not virus associated and occur during the course of the haematological disease, several years after the beginning. ANCA investigations are not helpful for the diagnosis of vasculitis in this context. Before diagnosing primary vasculitis, clinicians must be aware of vasculitis associated with infections, in particular, tuberculosis.

References