Systemic vasculitis with antineutrophil cytoplasmic autoantibodies (ANCA) in three dental technicians


1Service de médecine interne, Centre Hospitalier Universitaire Cochin, Paris; 2Département de néphrologie, Hôpital Louise Michel, Evry; 3Département de néphrologie, Centre Hospitalier Universitaire Necker, Paris; 4Service des maladies professionnelles, Centre Hospitalier Universitaire Cochin, Paris, France

Key words: vasculitis; dental technician; silica

Introduction

Silica exposure is known to induce various immune disorders. Systemic sclerosis (SS) was the first disease recognized to be associated with this environmental factor in stonemasons [1]. Although not completely established, the pathogenic role of silica has been strongly suggested, based on epidemiological data in SS and rheumatoid arthritis [2,3]. The association of silica exposure with other connective tissue diseases such as systemic lupus erythematosus (SLE), polymyositis, and undetermined autoimmune diseases is also probable [4,5]. On the other hand, rapidly progressive glomerulonephritis (RPGN) and systemic vasculitis were rarely reported in this context. During a 3-year period we observed three patients, dental technicians with occupational exposure to several kinds of dust, primarily silica, who developed systemic vasculitis associated with antineutrophil cytoplasmic autoantibodies (ANCA) (Table 1).

Case reports

Case 1*. A 59-year-old man who had been working as a dental technician for 43 years was admitted for evaluation of renal insufficiency. He presented with Raynaud’s syndrome and complained of a 4-kg weight loss over 4 months and fatigue. Two months before admission, serum creatinine was 145 μmol/l with microscopic haematuria and proteinuria (2.39 g/day). The erythrocyte sedimentation rate (ESR) was 100 mm in the first hour and C-reactive protein (CRP) was 107 mg/l. Thoracic radiographs showed diffuse micronodular opacities, especially in the upper fields. ANCA were detected by indirect immunofluorescence and a perinuclear staining pattern (p-ANCA) was noted. The level of antmyeloperoxidase (MPO) antibodies was 23 U/l as evaluated by enzyme-linked immunosorbent assay. Antinuclear antibody (ANA) was also positive (1/500), but anti-DNA and anti-ENA antibodies were not found. Serologies for HBV, HCV, and HIV were negative.

Histological evaluation of percutaneous renal biopsy revealed severe focal necrotizing glomerulonephritis with cellular crescents (Figure 1) with segmental fibrotic lesions, severe tubulointerstitial lesions, both

On physical examination at admission, bilateral acro-syndrome and livedo reticularis were observed. His blood pressure was 130/80 mmHg. Three days later he experienced right hemiparesis of sudden onset, which regressed within a few days. Serum creatinine was 477 μmol/l with microscopic haematuria and proteinuria (2.39 g/day). The erythrocyte sedimentation rate (ESR) was 100 mm in the first hour and C-reactive protein (CRP) was 107 mg/l. Thoracic radiographs showed diffuse micronodular opacities, especially in the upper fields. ANCA were detected by indirect immunofluorescence and a perinuclear staining pattern (p-ANCA) was noted. The level of antmyeloperoxidase (MPO) antibodies was 23 U/l as evaluated by enzyme-linked immunosorbent assay. Antinuclear antibody (ANA) was also positive (1/500), but anti-DNA and anti-ENA antibodies were not found.

Serologies for HBV, HCV, and HIV were negative. Histological evaluation of percutaneous renal biopsy revealed severe focal necrotizing glomerulonephritis with cellular crescents (Figure 1) with segmental fibrotic lesions, severe tubulointerstitial lesions, both

Correspondence and offprint requests to: Dr G. Grateau, Hôtel-Dieu de Paris, 1 Place du Parvis Notre-Dame, 75181 Paris Cedex 04, France.


© 1997 European Renal Association–European Dialysis and Transplant Association
Table 1. Characteristics of the three male dental technicians with vasculitis and antineutrophil cytoplasmic autoantibodies

<table>
<thead>
<tr>
<th>Cases</th>
<th>Age (years)</th>
<th>Duration of occupational exposure (years)</th>
<th>Clinical signs</th>
<th>Serum creatinine (mg/dl)</th>
<th>Treatment</th>
<th>Response to treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59</td>
<td>43</td>
<td>Fever, weight loss (4 kg) Raynaud’s phenomenon Cerebral infarction FNGN</td>
<td>53</td>
<td>Corticosteroid Cyclophosphamide</td>
<td>Attenuated</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>19</td>
<td>Polyarteritis Weight loss (8 kg) Raynaud’s phenomenon</td>
<td>24</td>
<td>Corticosteroid Cyclophosphamide</td>
<td>Attenuated</td>
</tr>
<tr>
<td>3</td>
<td>56</td>
<td>25</td>
<td>Fever, weight loss (3 kg) Myalgias</td>
<td>34</td>
<td>Corticosteroid</td>
<td>Attenuated</td>
</tr>
</tbody>
</table>

*Duration of occupational exposure to silica. FNGN, focal necrotizing glomerulonephritis; HD, haemodialysis; TR, transplantation.

Vasculitis in dental technicians

recent and old, and chronic vascular lesions; on one section leukocytoclastic vasculitis was seen. No deposits were detected by immunofluorescence. Computed tomography of the brain showed no cerebral haemorrhage, and magnetic resonance imaging exhibited multiple signals compatible with ischaemic lesions. The analysis of earlier thoracic radiographs revealed a progressive micronodular pattern from 1976 to 1992. The bronchial endoscopy was normal. Cultures were negative for Mycobacterium tuberculosis. Because of the patient’s occupational exposure, the diagnosis of silicosis was made. Pulse cyclophosphamide (750 mg/bolus) was begun and continued monthly for 1 year, combined with oral prednisone, starting at 1 mg/kg/day and progressively tapered. Eighteen months after beginning treatment, the patient was in good health, taking 10 mg of prednisone/day, and serum creatinine was stable at 180 μmol/l. Anti-MPO antibody levels decreased regularly and were under the detection threshold after 12 months of follow-up.

Case 2. A 37-year-old dental technician who had exercised his profession for 19 years was referred to our hospital for renal insufficiency. He had a recent history of polyarthritis, an 8-kg weight loss over 2 months and unilateral Raynaud’s phenomenon. On physical examination, blood pressure was 130/80 mmHg. Serum creatinine was 216 μmol/l and a urinalysis revealed microscopic haematuria (300 000 RBC/ml) and proteinuria (3.9 g/day). The ESR was 96 mm in the first hour and CRP was 64 mg/l. Thoracic radiographs were normal. Renal angiography demonstrated microaneurysms in the upper poles of both kidneys. p-ANCA staining was positive and the level of anti-MPO antibodies was 30 U/l. Serologies for HBV, HCV and HIV were negative. A percutaneous renal biopsy was performed and showed necrotizing crescentic glomerulonephritis. No vascular lesions and no immune deposits were observed. Pulse cyclophosphamide (1200 mg/bolus) was begun and continued monthly for 1 year in combination with oral prednisone, starting at 1 mg/kg/day, and progressively tapered. Despite this intensive treatment, the disease was never completely controlled. Urinary sediment remained active and proteinuria reached nephrotic range and progressed to renal failure. ANCA never fell below the detection threshold. Iterative renal biopsies showed further degradation of renal lesions. Two years after the beginning of treatment, periodic haemodialysis was started and the patient subsequently received a renal graft.

Case 3. A 56-year-old man who had been working as a dental technician for 25 years was admitted for evaluation of renal insufficiency. He complained of a recent 3-kg weight loss over 2 months with diffuse myalgias and a transient low-grade fever. Three months earlier, he had suffered from acute diarrhoea and had been hospitalized. A coloscopy had discovered two polyps, which were resected. Histological examination showed tubular villous adenomas with no signs of malignancy. Serum creatinine was 297 μmol/l, proteinuria was 1.45 g/l and microscopic haematuria was noted. On physical examination, blood pressure was 130/80 mmHg and a slight systolic heart murmur was detected. Serum creatinine was 306 μmol/l, proteinuria 1.2 g/day and microscopic haematuria persisted. ESR was 124 mm at the first hour and CRP was 65 mg/l. Thoracic radiographs showed a weak interstitial pattern. The search for p-ANCA was positive and the level of anti-MPO antibodies was 28 U/l. Serologies for HBV, HCV and HIV were negative. A percutaneous renal biopsy was performed and showed focal necrotizing glomerulonephritis with primarily old crescents; only 12% of the glomeruli had recent necrotic lesions. There were also severe and diffuse old tubulointerstitial and vascular lesions, but only one lesion of arteriolar vasculitis was observed. No hypercellularity was found in bronchoalveolar lavage fluid. Pulse methylprednisolone was begun and followed by prednisone (1 mg/kg/day). One month later, serum creatinine was unchanged, but general signs had disappeared.
Discussion

We report here on three dental technicians who presented evidence of systemic vasculitis with ANCA, an association that does not seem to be coincidental. The vascular diseases seen in these patients would be classified as periarteritis nodosa according to the ACR 1990 classification of vasculitis [6]. However, according to the Chapel Hill nomenclature [7] they are considered to be microscopic polyangiitis, since its definition of polyarteritis nodosa excludes glomerular involvement, even in the presence of microaneurysms, as in patient 2. Our three cases worked exclusively in their laboratories and had no professional contact with dentists’ patients. Serologies for HBV, HCV, and HIV were negative. The evolution of the renal involvement in these three individuals was quite different. In the first patient, renal disease was controlled and remained stable 12 months after the discontinuation of cyclophosphamide therapy. The outcome of renal disease in the second patient was poor, possibly because the treatment was delayed. In the third patient, the renal biopsy revealed old lesions, and short-term treatment with prednisone induced no changes of serum creatinine, while general signs were markedly attenuated. ANCA kinetics paralleled clinical evolution. ANCA levels decreased regularly to become undetectable in the first patient, whereas they fluctuated and never fell below the detection threshold in the second patient. However, the predictive value of ANCA changes on disease activity in systemic vasculitis is disputed [8].

Dental technicians are exposed to various types of dust, such as silica, alloys, or acrylic plastics, which may induce pneumoconiosis and other lung diseases [9]. Several connective-tissue diseases have been described in association with silica dust exposure, with or without silicosis, particularly in dental technicians [9]. One of our patients had positive ANA, but p-ANCA fluorescence can resemble that of ANA, and this patient did not have criteria for SLE [10]. Moreover, in a case-control study, the prevalence of autoantibodies (antinuclear antibodies, antihistone antibodies) and rheumatoid factors was not higher in dental technicians than in controls [9]. RPGN has also been reported in patients with silica exposure, mainly in miners [11,12]. Recently, the association of RPGN with p-ANCA anti-MPO antibodies and various sources of silica exposure was corroborated by a case-control study [13]. However, there were no dental technician among the workers exposed to silica in that article. To date and to the best of our knowledge, only two cases of RPGN in dental technicians have been reported [14,15]. In the first case there were no signs of extrarenal vasculitis; in the second RPGN was preceded by membranous glomerulopathy and the patient also had Ehlers-Danlos syndrome type III. The existence of ANCA was not determined in either case. Recent findings in a case-control study supported the association of Wegener’s granulomatosis with various products containing silicon, and among them silica [16]. Although this epidemiological report does not definitely prove that silica exposure is associated with increased risk for vasculitis, it associated two different silicon products with the same risk. It is of note that the association of an organic silicon-containing product, silicone, with the risk of connective-tissue disease is still disputed [17]. However, the occurrence of vasculitis in this latter context has not been described.

The pathophysiology of vasculitis remains unclear and the direct pathogenic role of ANCA is disputed. The recent development of a rat model for anti-MPO-associated RPGN may further the study of this form of vasculitis [18]. It may also enhance our understanding of the possible role of silicon exposure in autoimmune diseases. Our three case histories are in agreement with, but do not definitely prove the hypothesis of, a relationship between systemic vasculitis and occupational exposure to silica dust. Further case-control studies are required to prove this hypothesis.

References

9. Choudat D, Triem S, Weill B et al. Dental technicians are exposed to various types of dust, such as silica, alloys, or acrylic plastics, which may induce pneumoconiosis and other lung diseases. Am J Kidney Dis 1987; 9: 224–230
15. Sauvaert P, Pairet JC, Rostocker J, Belghiti D, Brochard P. Les glomerulonéphrites induites par une exposition profes-
Vasculitis in dental technicians

- Sionnelle à la silice; mise au point à partir d’une observation. Arch Mal Prof 1991; 51: 593–595

Received for publication: 15.5.96
Accepted in revised form: 26.9.96