Meningeal involvement in apparently ANCA-negative Wegener’s granulomatosis: a role for PR3 capture-ELISA?

Sir, Central nervous system (CNS) involvement is rare in Wegener’s granulomatosis (WG): the spectrum of CNS manifestations includes cerebrovascular events, seizures and cranial nerve abnormalities [1, 2]. Meningitis is exceedingly rare, and its diagnosis often challenging [1–3].

A 57-yr-old man was admitted to hospital because of untreatable headache, photophobia, neck stiffness and paranasal sinus pain. Eight years earlier, WG had been diagnosed because of inflammatory involvement of the upper (sinusitis, anosmia) and lower (pulmonary nodules, histologically showing granulomas with giant cells and necrotizing vasculitis) respiratory tract, associated with high ESR and cytoplasmic-ANCA (C-ANCA), which were anti-proteinase 3 (PR3) (103 EU/ml, normal <20) by routine ELISA. Cyclophosphamide (CYC) and prednisolone (PDN) therapy was successfully conducted for 2 years.

On admission, ESR (75 mm/Ih) and CRP (116 mg/l; normal <5) were high. ANCAs tested negative using indirect immunofluorescence (IIF) (ZenTech, Angleur, Belgium) and antigen-specific, direct-ELISA for PR3 and myeloperoxidase (Fenning BioMed GmbH, Germany).

Head CT showed mucosal thickening of the maxillary sinuses and turbinates without bone erosions. Brain MRI disclosed dural thickening, particularly of the tentorium cerebelli and the posterior portion of the falx; these sites showed pronounced contrast-enhancement (Fig. 1A and D). Moderate dural thickening and enhancement were also observed along the petrous bone and the cavernous sinuses. The meninges adjacent to the orbital, nasal and paranasal areas were normal.

Cerebrospinal fluid (CSF) analysis revealed pleocytosis (WBC count 32/mm³, predominantly lymphocytes), but normal protein and glucose levels; CSF cultures were negative for viruses, bacteria and fungi. CSF cytology was unremarkable. Part of the patient’s serum obtained on admission had been stored at −80°C, thus we used it to recheck ANCAs using PR3-capture ELISA (Phadia, Freiburg, Germany), which, unlike the routine assay, showed strongly positive PR3-ANCAs (121 AU/ml, normal <7). CSF analysis by routine techniques and capture-ELISA was negative for ANCA. Chest CT ruled out lung involvement.

A WG relapse with upper airway tract and meningeal involvement was thus diagnosed, and PDN (1 mg/kg/day) plus CYC (1.5 mg/kg/day) therapy was started. The cranial symptoms resolved within 10 days, and MRI also revealed a reduction in meningeal thickening and contrast-enhancement (Fig. 1B and E). The treatment was continued for a 12-month period, at the end of which the meningeal abnormalities disappeared (Fig. 1C and F).

The frequency of meningitis ranges between 0% and 7% of WG cases [1, 2]. WG-related meningitis can result from cerebral vessel vasculitis, direct invasion from adjacent sites or intraparenchymal granulomas [1]. Our patient had neither erosive bone lesions of the paranasal sinuses nor CNS granulomas, so meningeal vasculitis was the most likely pathogenetic mechanism.

WG is usually associated with C-ANCA; the sensitivity of ANCA-testing can be as high as 100% in patients with active-generalized disease, and the positivity of PR3-ANCA approaches a specificity of 90% [2]. However, patients with WG apparently limited to the upper respiratory tract are frequently ANCA-negative and, more importantly, up to 83% of these...
ANCA-negative cases have severe underlying CNS involvement [4–6]. This prevalence is high if we consider that only 5–10% of WG patients were shown to have CNS disease in large cohorts [6]. Therefore, ANCA-negative WG may hide remarkable CNS involvement [5].

In our patient, WG initially presented as a systemic disease and C-ANCA (anti-PR3) tested positive using routine IIF and direct-ELISA. At the time WG relapsed with upper airway tract and meningeal involvement, ANCA were negative on routine assays. Surprisingly, PR3-capture ELISA detected strongly positive PR3-ANCAs. PR3-capture ELISA uses, as a capturing ligand for PR3, a mouse monoclonal antibody (MoAb 4A3) directed to a PR3 epitope that is rarely targeted by human ANCs. The PR3 epitopes may be more accessible using this assay, which is also thought to better preserve the conformation of PR3 [7]. In the first clinical evaluation of this capture-ELISA, its diagnostic sensitivity was higher compared with C-ANCA by IIF in patients with WG-related renal disease [7]. Recently, a multicentre evaluation of capture-ELISA compared with direct-ELISAs and IIF confirmed the higher sensitivity of capture-ELISA [8]. Moreover, detection of PR3-ANCA by capture-ELISA showed a higher sensitivity than that obtained by direct-ELISA in diagnosing relapse during the follow-up of vasculitis [9]. The superiority of PR3-capture ELISA could be due to analytical reasons or to its ability to detect PR3-ANCA/PR3 immune complexes [10].

Meningitis is a rare and insidious complication of WG and it may be difficult to distinguish from meningeal involvement secondary to neoplasms or infections, particularly in immunosuppressed patients. In such cases, finding positive PR3-ANCAs can be useful to steer the diagnosis towards a WG manifestation. This is also why a more sensitive assay, such as PR3-capture ELISA, should be included in the diagnostic armamentarium of apparently ANCA-negative WG cases, particularly when atypical clinical presentations make the diagnosis more challenging. Like in our case, if diagnosed early, WG-related meningitis usually responds to immunosuppressive therapy, whereas if left untreated it can cause severe and life-threatening complications.

Acknowledgement

The authors gratefully acknowledge Dr P. Schianchi for his help in preparing the figures.

The authors have declared no conflicts of interest.

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Accepted 21 March 2007

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Rheumatology 2007;46:1376–1377
doi:10.1093/rheumatology/kem086
Advance Access publication 19 June 2007

Spontaneous Pneumo-mediastinum in systemic sclerosis—a case report

The leading cause of mortality in systemic sclerosis (SSc) is now pulmonary disease. This is the first report of spontaneous pneumo-mediastinum in SSc, although spontaneous pneumothorax has been previously described [1].

A 52-yr-old male ex-smoker with rapidly progressive SSc and pulmonary fibrosis presented with severe breathlessness. He had extensive skin thickening of face and arms, was malnourished, afebrile, and pulmonary arterial pressure was normal. He had extensive pulmonary disease. This is the first report of spontaneous pneumo-mediastinum in SSc patient. Abnormal collagen formation and cigarette smoking possibly contributed to sub-pleural bullae formation and severe breathlessness. Pulmonary function tests were stable with a restrictive pattern, and pulmonary arterial pressure was normal. He had extensive skin thickening of face and arms, was malnourished, a- febrile, pulse 130/min, respiration 30/min, arterial blood gas showed oxygen saturation of 92% on room air. There was reduced air entry in lung fields, but no mediastinal crepitus. CT scan of thorax showed stable fibrotic changes with free air in the anterior mediastinum and several sub-pleural bullae (Fig. 1). Pneumo-mediastinum was diagnosed which resolved completely with conservative management. This is the first case-report of pneumo-mediastinum in a SSc patient. Abnormal collagen formation and cigarette smoking possibly contributed to sub-pleural bullae formation and severe breathlessness. Pulmonary function tests were stable with a restrictive pattern, and pulmonary arterial pressure was normal. He had extensive skin thickening of face and arms, was malnourished, afebrile, pulse 130/min, respiration 30/min, arterial blood gas showed oxygen saturation of 92% on room air. There was reduced air entry in lung fields, but no mediastinal crepitus. CT scan of thorax showed stable fibrotic changes with free air in the anterior mediastinum and several sub-pleural bullae (Fig. 1). Pneumo-mediastinum was diagnosed which resolved completely with conservative management.

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FIG. 1. CT scan of Thorax showing Pneumo-mediastinum.