LETTERS

Antibodies to α-fodrin derived peptide in Sjögren's syndrome

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Sjögren's syndrome (SS) is a chronic autoimmune disorder of unknown cause. Haneji *et al* identified a 120 kDa fragment of the ubiquitous cytoskeletal protein α-fodrin as an autoantigen in an NFS/sld mouse model of human SS.[1] More recently, the sensitivity and specificity of α-fodrin antibodies in SS in several studies suggested that it might be of value in the diagnosis of SS.[1–3] In the present study, a conserved motif, rather than the whole protein, in α-fodrin was used as antigenic peptide to define further the role of anti-α-fodrin antibodies in SS. This is the first study so far to evaluate the prevalence of anti-α-fodrin peptide antibodies (α-FPA) in a cohort of Chinese patients with SS.

Serum samples from 89 patients with SS (85 female, 4 male; 74 with primary SS (pSS) and 15 with secondary SS (sSS) associated with rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE)) were examined. Their mean (SD) age was 54 (6.5) years, and the mean (SD) disease duration was 6.6 (3.8) years. A few patients were receiving steroids or immunosuppressive drugs. Serum samples from 41 patients with SLE, 44 with RA, and 59 healthy subjects were analysed as controls. All the patients with SS were carefully evaluated based on the European-American criteria.[4] Patients with RA and SLE fulfilled the American College of Rheumatology (ACR) criteria for classification. A sequence of the α-fodrin derived peptide (RQKLEDSYRFQFFQRDAEEL)[1] was synthesised by a solid phase technique on an Applied Biosytems Peptide Synthesizer. Synthesised α-fodrin peptide was used as substrate in an enzyme linked immunosorbent assay (ELISA) to detect IgG α-FPA in serum samples of the patients and the controls.

The IgG α-FPA were present in 54/74 (73%) patients with primary SS, 6/15 (40%) with secondary SS, 18/41 (20%) with SLE, 13/44 (30%) with RA, and 2/59 (3%) normal blood donors (table 1). The prevalence of α-FPA in primary and secondary SS was significantly higher than in SLE, RA, and normal controls ($p<0.01$ in each case).

The sensitivity and specificity of α-FPA in SS were 73% and 88.7%, respectively. The sensitivity of α-FPA in pSS was much higher than anti-SSA, anti-SSB, and antinuclear antibodies (ANA; table 2). The specificity of α-FPA (81.8%) was similar to that of anti-SSB (85.0%), and was higher than that of anti-SSA (64.7%) and ANA (42.6%) in the diagnosis of pSS. A high prevalence of α-FPA was found in patients with SS who lacked anti-SSA, anti-SSB, and ANA. The presence of α-FPA was closely associated with extraglandular manifestations, such as pulmonary fibrosis, renal failure, and vasculitis.

Previous studies have shown that the antigenic epitope of α-fodrin is within the amino terminal region and masked in the entire amino acid sequence. To analyse the significance of α-fodrin antibodies in SS, a conserved α-fodrin peptide was used as the antigen in this study. The results suggest that α-FPA are a serological variable in SS, and are more sensitive than ANA, anti-SSA, and anti-SSB. α-FPA appear in the early stage of SS, indicating that these antibodies are valuable for early diagnosis of the disease. We have also shown that α-FPA are associated with pulmonary interstitial fibrosis, vasculitis, and renal disease, which suggests that α-FPA has a pathogenic role in SS.

The 120 kDa α-fodrin is abundant in the epithelial cells of the human salivary gland and can stimulate peripheral blood T cells in patients with SS.[5] It is suggested that α-fodrin may undergo a redistribution and relocate to the cell membrane of apoptotic cells in human SS.[6] The autoantigen on the surface of apoptotic cells is involved in antigen presentation processing and induction of autoantibodies. We speculate that cleavage and altered distribution of α-fodrin in glandular epithelial cells may impair the secretory function and perpetuate an autoimmune response to α-fodrin, leading to production of autoantibodies and glandular destruction in SS.

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Table 1 Prevalence of α-FPA in patients with SS, RA, and SLE

	Patients	α-FPA	
	(n)	Positive No (%)	OD Values Mean (SD)
SS	89	60 (67)	0.30 (0.08)
Primary SS	74	54 (73)	0.29 (0.08)
Secondary SS	15	6 (40)	0.34 (0.09)
SLE	41	8 (20)†	0.23 (0.09)*
RA	44	13 (30)	0.28 (0.09)
Healthy controls	59	2 (3)†	0.17 (0.04)*

*$p<0.05$; †$p<0.01$ in comparison with the group with SS.

Table 2 Sensitivity and specificity of α-FPA in 74 patients with primary SS

Antibodies	Positive (n)	Sensitivity (%)	Specificity (%)
α-FPA	54	73.0*	81.8†
Anti-SSA	38	51.4	64.7
Anti-SSB	9	12.2	85.0†
ANA	47	63.5	42.6

*$p<0.01$, compared with anti-SSA, anti-SSB, and ANA; †$p<0.05$, compared with anti-SSA and ANA.

Competing interest: None.

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REFERENCES

1 **Haneji N**, Nakamura T, Takio K, Yanagi K, Higashiyama H, Hayashi Y. Identification of alpha-fodrin as a candidate autoantigen in primary Sjögren's syndrome. *Science* 1997;**276**:604–6.
2 **Maeno N**, Takei S, Imanaka H, Oda H, Yanagi K, Hayashi Y, *et al.* Anti-alpha-fodrin antibodies in Sjögren's syndrome in children. *J Rheumatol* 2001;**28**:860–4.
3 **Witte T**, Matthias T, Oppermann M, Helmke K, Tishler M, Schmidt RE, *et al.* Prevalence of antibodies against alpha-fodrin in Sjögren's syndrome: comparison of 2 sets of classification criteria. *J Rheumatol* 2003;**30**:2157–9.
4 **Vitali C**, Bombardieri S, Jonsson R, Alexander EL and the European Study Group on Classification Criteria for Sjögren's syndrome. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Group. *Ann Rheum Dis* 2002;**61**:554–8.
5 **Yanagi K**, Ishimaru N, Haneji N, Saegusa K, Saito I, Hayashi Y. Anti-120-Kd alpha-fodrin immune response with Th1-cytokine profile in the NOD mouse model of Sjögren's syndrome. *Eur J Immunol* 1998;**28**:3336–45.
6 **Nagraju K**, Cox A, Casciola-Rosen L, Rosen A. Novel fragments muscarinic acetylcholine receptor generated during cytotoxic lymphocyte granule-induced cell-death. *Arthritis Rheum* 2001;**44**:2376–86.

"Bubbles in the brain": an unusual complication of dermatomyositis

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Dermatomyositis (DM) is an inflammatory microangiopathy, affecting particularly the skin and muscles. The incidence ranges from 0.2 to 1.0/100 000; an overlap with other connective tissue diseases such as systemic sclerosis has been described, as has an association with cancer. Clinically DM is identified by a characteristic rash and a varying muscle weakness. The clinical diagnosis is confirmed by typical muscle histology.[1]

A 60 year old man was admitted to our department with a 2 week history of muscle weakness, myalgias, dysphagia, a heliotrope rash on the eye lids, and bilateral acral finger ulcers. Creatine kinase (3879 U/ml, normal <171 U/ml) and C reactive protein (170 mg/l; normal <5 mg/l) were raised; autoantibodies (antinuclear antibodies (ANA), extractable nuclear antigen (ENA), anti-synthetase antibodies, rheumatoid factor, antineutrophil cytoplasmic antibodies (ANCA)) were negative. A muscle biopsy showed perivascular inflammation, an infiltrate predominantly of CD4+ T cells, and perifascicular atrophy, confirming the suspected diagnosis of DM. Despite the advanced age of the patient, the rapid onset of the manifestations, and the lack of autoantibodies, cancer associated myositis could be ruled out. Consequently, corticosteroid treatment (1 mg/kg body weight (b. wt)) was started.

The patient developed a fever, and a chest *x* ray examination showed a skin emphysema and a pneumomediastinum. Computed tomography (CT), oesophagoendoscopy, and bronchoscopy disclosed no cause of the pneumomediastinum. In particular, again no gastrointestinal or intrapulmonary tumour, pneumothorax or fistula was found. The patient then complained of dizziness, position dependent headache, and neck stiffness; after a syncope his mental state was altered. CT ruled out a cerebral infarction or bleeding, but showed intracranial air inclusions (fig 1). No signs of a fracture were seen at the base of the skull, but magnetic resonance imaging (MRI) of the neck showed a spondylodiscitis with a paravertebral inflammation between cervical spine C5–7 (fig 2A). CT performed after swallowing a contrast agent detected a fistula containing air from the hypopharynx into the paravertebral region (fig 2B). To obtain a detailed evaluation an inflexible endoscopy was performed, showing two ulcers and a covered perforation of the upper oesophagus.

We assumed that disease activity was uncontrolled and the oesophagus was affected, and higher doses of corticosteroids (2 mg/kg b. wt) and immunoglobulins (1 g/kg b. wt) were given. Because of the spondylodiscitis and the proof of bacteria in the cerebrospinal fluid a further immunosuppression was postponed and intravenous antibiotic treatment was started. The patient was discharged weeks later without any neurological sequelae. Two years later he died from fatal

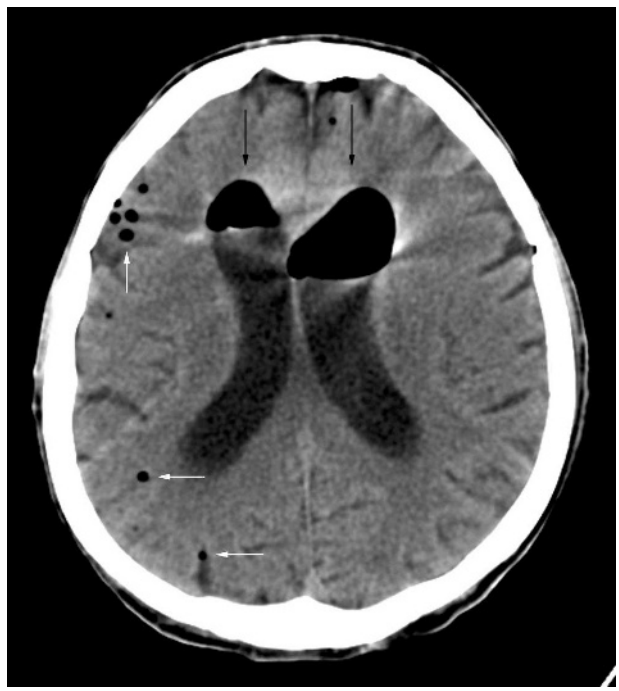

Figure 1 A CT scan of the head shows the intracranial air inclusions preferentially in the lateral ventricles (black arrows), but also disseminated in the subarachnoid space (white arrows).