

## Hodgkin's disease occurring in primary Sjögren's syndrome

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### Abstract

**A 57 year old woman with a 13 year history of mouth dryness, keratoconjunctivitis sicca, and recurrent bronchial infections presented with multiple lymphadenopathies. Histological diagnosis was Hodgkin's disease. B and T cell lymphomas are well known complications of Sjögren's syndrome. This case provides evidence that Hodgkin's disease may also be associated with this syndrome.**

Lymphoma and pseudolymphoma are occasional complications of primary and secondary Sjögren's syndrome.<sup>1-3</sup> Most of these lymphomas are derived from B lymphocytes,<sup>4</sup> a fact which supports the previous hypothesis that a chronic state of immunological hyperactivity may be responsible for the transition from a polyclonal cellular infiltrate to a monoclonal neoplasm.<sup>5</sup>

T cell lymphoma occurring in Sjögren's syndrome is unusual, both in primary and secondary Sjögren's syndrome,<sup>6,7</sup> and has only recently been described. The precise mechanism or a possible cause and effect relation between Sjögren's syndrome and T cell lymphoma are unknown at present.

This case report records the occurrence of malignant Hodgkin's lymphoma in a patient with histological and clinic evidence of Sjögren's syndrome. We do not offer any explanation for this association that has seldom been reported.<sup>8</sup>

### Case report

The patient, a 58 year old woman, was referred to us for evaluation of swelling of both parotid glands that had appeared seven months earlier, associated with persistent mouth dryness and arthralgias of the elbows, wrists, and small joints of the hands. She also had a 13 year history of keratoconjunctivitis sicca (that required methylcellulose eyedrops), recurrent bronchial infections, pharynx dryness, and had had occasional painful oral ulcers.

On examination the patient was afebrile and normotensive. The skin was dry. Prominent swelling of both parotid glands and severe mouth dryness were evident. An aortic grade II/IV systolic murmur and bilateral basal pulmonary crackles 'Velcro' type were heard. The spleen was palpated 3 cm below the costal margin and the liver seemed normal. Some lymphadenopathies were detected in both axillar regions, of a size up to 3 cm in diameter, freely movable, and mildly painful to palpation. Examination by an ophthalmologist showed diminished tear production (Schirmer tear test 4 mm/5 min for the right eye and 7 mm/5 min for the left one) and keratitis punctate in the rose

bengal test. The rest of the physical examination, including locomotive and neurological systems, was unremarkable. A minor salivary gland biopsy, obtained through apparently normal lip mucosa, was done. Histological examination of the specimen showed focal lymphocytic infiltration, with two foci per 4 mm<sup>2</sup> of gland area.

Blood studies showed haemoglobin 140 g/l, leucocyte count  $9.8 \times 10^9/l$ , platelets  $195 \times 10^9/l$ , and erythrocyte sedimentation rate 14 mm/h. The results for routine biochemical indices were normal, as were the coagulation profile and urine analysis findings. The total plasma protein was 65 g/l, with a reduction in the gammaglobulin fraction (4.3 g/l) as the only abnormality in the protein profile. Immunoglobulin concentrations were IgG 6.15 g/l, IgA 0.61 g/l, and IgM 0.86 g/l. Electrophoresis of a specimen of concentrated urine was normal. The serum  $\beta_2$  microglobulin concentration was 5.1 mg/l (normal <3) and the total 24 hour urine excretion was 0.214 mg (normal <0.360). C3 and C4 components of complement were normal. Rheumatoid factor, the Venereal Disease Research Laboratory test, Coombs' test, and cryoglobulins were negative. Antinuclear antibodies were positive at a titre of 1/80 (indirect immunofluorescence standard technique on HEP<sub>2</sub>). Studies for anti-Ro, anti-La (gel immunodiffusion with primate spleen extract as antigen), anti-RNP, antithyroid, anti-mitochondrial antibodies, and anti-dsDNA were negative, as were the serological tests for *Brucella* spp, *Salmonella* spp, virus B, Epstein-Barr virus, human immunodeficiency virus, and toxoplasma.

Cutaneous tests for delayed hypersensitivity (Multitest; Institute Merieux, Lyon, France) were negative for all antigens tested. An electrocardiogram and a two dimensional echocardiogram disclosed no abnormalities.

An x ray examination of the chest showed a normal cardiac silhouette, enlarged right hilum with polycyclic margin, and bilateral basal interstitial infiltrate with predominant nodular pattern (figure). Radiographs of the hands were normal. Computed tomographic scans of the thorax and abdomen showed multiple lymphadenopathies at supraclavicular, axillar, paratracheal, and tracheobronchial locations. Lung hilar lymph nodes on both sides were also affected, as were the coeliac and para-aortic lymph nodes. Interstitial infiltration of the lungs and splenomegaly was also confirmed.

Pulmonary function studies showed moderate hypoxaemia (Po<sub>2</sub> 56 mmHg), mild hyperventilation (PCO<sub>2</sub> 33 mmHg), and an alveolar-arterial oxygen difference of 43 mmHg. Spirometry showed forced vital capacity 2000 ml

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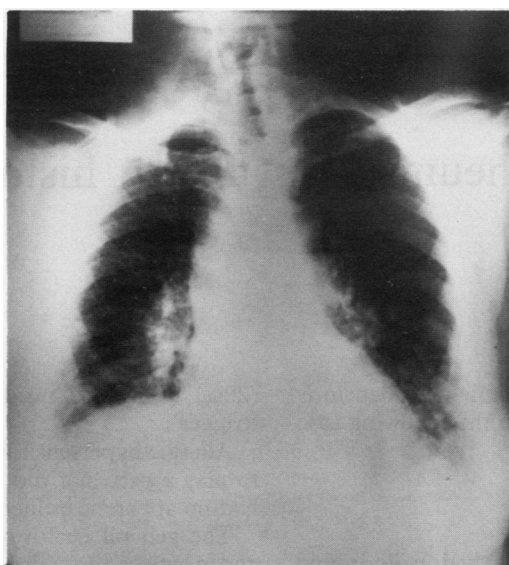
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Accepted for publication  
10 October 1989

Figure 1: x Ray picture of the chest showing an enlarged right hilum and bilateral basal interstitial infiltrate with predominant nodular pattern.



(71%), without obstruction. Transfer factor of the lung for carbon monoxide, as determined by the single breath method, was normal. Stains and cultures for microorganisms and a search for cytological abnormalities in sputum were negative. A fiberoptic bronchoscopy and some transbronchial lung biopsy specimens were unremarkable.

Surgical excision of one axillar lymph node was performed. Microscopic examination showed loss of the normal architecture of the node; diffuse infiltration by lymphocytes, histiocytes, and eosinophils that extended out of the capsule; multiple mitosis and typical Reed-Sternberg cells.

The patient was diagnosed as having Hodgkin's disease of lymphocytic predominance, stage IIIA<sub>2</sub> (or IVA with lung disease, though this extralymphatic location could not be histologically proved) and was aggressively treated with a combination of cyclophosphamide, vincristine, procarbazine, and prednisone. Initial results have shown a considerable decrease in the number and size of the lymphadenopathies and splenomegaly and improvement in the chest radiograph abnormalities. General status and respiratory symptoms have also improved, but the benefit for the sicca complaints and parotid swelling has been slight.

### Discussion

Sjögren's syndrome is characterised histologically by mononuclear cellular infiltration of the salivary and lacrimal glands, and serologically by the presence of many tissue component antibodies. Since the report of Talal in 1964<sup>1</sup> many investigators have emphasised the correlation between Sjögren's syndrome and the development of malignant lymphoma. It has been suggested that this association may be due to a chronic state of immunological hyperactivity, both in the usual case of B cell lymphoma<sup>5,9</sup> and in the rare patients with T cell lymphoma.

To the best of our knowledge a report of only one patient with definite Hodgkin's disease occurring in Sjögren's syndrome has been published.<sup>8</sup> Other descriptions of the association of Sjögren's syndrome and Hodgkin's disease have been doubtful<sup>5</sup> or not reported (cited in ref 1).

The criteria which we used to arrive at the diagnosis of Sjögren's syndrome deserve some comment. Although objective tests for assessing the salivary component were not performed, some disagreement exists as to the validity of these tests.<sup>10</sup> Moreover, one author has suggested that the salivary component of Sjögren's syndrome be diagnosed based on a focus score >1 on labial salivary gland biopsy as the sole criterion.<sup>11</sup> Serum autoimmune markers of patients with Sjögren's syndrome often change and even disappear at the time of malignant transformation, coinciding with a decline in serum immunoglobulins.<sup>1,5,6,12</sup> This might explain the fairly low titre of antinuclear antibodies in our patient. Anyway, most authorities do not consider the evidence of autoimmune disease as an indispensable condition for the diagnosis of Sjögren's syndrome.<sup>13</sup>

When the patient was first seen by us signs of advanced lymphoma were evident. Hodgkin's disease can infiltrate the lacrimal and salivary glands,<sup>14</sup> and, in fact, pre-existing lymphoma is a formal exclusion for the diagnosis of Sjögren's syndrome.<sup>15</sup> In our patient the long history of ocular and oral symptoms and the absence of atypical or malignant cells on salivary gland biopsy refute this possibility.

We do not provide any explanation or causal relation for the association of Sjögren's syndrome and Hodgkin's disease. The cause of Hodgkin's disease is an intriguing question, still unsolved, that has been considered in many papers. Our report raises the possibility that Sjögren's syndrome increases the risk of Hodgkin's disease and emphasises the need for monitoring of these patients for the development of malignant lymphoma.

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