

## KERATO-CONJUNCTIVITIS SICCA AND THE COLLAGEN DISEASES\*

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KERATO-CONJUNCTIVITIS sicca is more often seen by and is of more interest to the ophthalmologist than the physician. It is little known and yet not uncommon. The usual syndrome is one affecting mainly middle-aged women and consisting of kerato-conjunctivitis sicca, rhinitis sicca, xerostoma, pharyngitis sicca, and parotid enlargement, and frequently including a chronic polyarthritis (Sjögren's syndrome). The aetiology is obscure, and from time to time such conditions as endocrine glandular dysfunction, focal sepsis, bacterial infection, virus infection, allergy, and vitamin deficiency have been put forward as possible factors. Association of this type of conjunctivitis has been noticed to occur in conditions which are recognized to be themselves of the same family.

The investigations carried out in all cases included haemoglobin estimation, blood count and differential white blood cell count, erythrocyte sedimentation rate, and Wassermann reaction, and Kahn test. X rays were taken of the chest, parotid glands, and joints, when the latter were affected. Blood urea, serum protein, and liver function tests were carried out.

In the last four cases, because of the related generalized disease, there were extensive investigations. These varied slightly from case to case, but included, in addition to the above: sternal marrow biopsy, blood and urine cultures, serum agglutinins for *B. abortus*, etc., blood pyruvic acid, serum electrolytes, serum phosphorus and calcium, renal function tests, creatine excretion, urinary coproporphyrins, and electrocardiography.

### Case Reports

The two following cases are typical examples of Sjögren's syndrome and illustrate the usual clinical and laboratory findings.

**Case 1, a married woman, aged 55 years**, was seen on September 16, 1954, and investigated as an out-patient. There was a history of having had a polyarthritis for 6 years with recurrent exacerbations and remissions. A constant irritation of the eyes with a sensation of grit in them had been noticed for 6 months, and a dry mouth and tongue had been present for 2 months.

The patient was of stout build. The positive clinical features were a rheumatoid arthritis, xerostoma and dryness of the tongue, slight prominence of the left parotid, and typical kerato-conjunctivitis sicca. Schirmer's test (Schirmer, 1903) showed deficient tear secretion. Rose Bengal (Rose, Luttmann, and Houghton, 1950) produced characteristic staining of the conjunctivae.

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**Case 2, a married woman, aged 53 years,** was first seen on September 16, 1954, and investigated as an out-patient. She had had recurrent attacks of arthritis since 1926, but had only become handicapped 18 months previously. For 6 months there had been a sensation of grit in the eyes and the vision had been deteriorating. She complained of a dry mouth and tongue. There had been dyspepsia with irregular upper abdominal discomfort and flatulence intermittently for over 2 years.

She was of spare build. She had typical rheumatoid arthritis in the hands, wrists, elbows, shoulders, ankles, and knees. There was kerato-conjunctivitis sicca. Schirmer's test was positive. There was no parotid enlargement, and the tongue was moist. Examination of the cardiovascular system showed a mitral stenosis. There was some chronic bronchitis and emphysema.

In the above two cases the erythrocyte sedimentation rate was moderately increased, the blood showed a moderate degree of normocytic hypochromic anaemia, and x rays confirmed arthritic joint changes of rheumatoid type. The blood urea was at the outer limits of normal and in one case the serum globulin was relatively increased. The total serum proteins were of normal value.

The following cases show this eye condition associated and concurrent with other diseases.

**Case 3, an unmarried woman, aged 50 years,** was admitted to hospital on October 15, 1953, with a history of paraesthesia and numbness of the feet and legs of gradually progressive type and accompanied by severe pain in the legs. A pyrexia had been discovered. She had had measles and chickenpox in infancy.

The clinical signs were paralyses, muscular wasting, and sensory changes suggestive of a polyneuritis. The further observation suggested that this polyneuritis was due to polyarteritis nodosa. Parotid gland enlargement was seen on October 28, particularly prominent on the right side. Xerostoma was noted. The parotid enlargement subsided a month later co-incident with treatment by cortisone, but recurred 2 months later. From November 10 she complained of painful eyes and these showed the typical appearances of kerato-conjunctivitis sicca. There was staining by Rose Bengal. Schirmer's test was positive. The parotid enlargement became prominent during May, 1954, and persisted until death. There was a progressive muscular weakness and wasting over a period of 9 months and the patient died on July 21, 1954. The *post-mortem* examination confirmed the clinical diagnosis of polyarteritis nodosa.

**Case 4, an unmarried woman, aged 40 years,** was first admitted to hospital in March, 1946, with an illness showing appearances in keeping with scleroderma and rheumatoid arthritis of the hands. There was in addition a past history of haematemesis and dyspepsia and x rays had shown a duodenal ulcer. She had had Raynaud's phenomenon (Raynaud, 1862) in her early twenties which had disappeared after 6 years. She was again admitted on April 1, 1954, and at that time complained of increased pain and stiffness of the fingers for 2 months before admission, during which time the tips of the fingers had become black and shrunken. She had noticed dryness of the mouth and hoarse voice some 6 years ago and 2 years ago there had been swelling of the parotid glands which became maximal in 6 months and remained static thereafter. Tightness of the skin around the mouth had become prominent a year ago and at the same time she had a sensation of grit in the eyes.

She was a small spare pale woman with scleroderma of the fingers and early gangrene of their tips. There was bilateral enlargement of the parotid glands. The mouth and tongue were dry. The buccal opening was small and the surrounding skin fissured. The conjunctivae were red and fiery-looking and showed typical staining with Rose Bengal. Schirmer's test was positive. There was in addition a polyarthritides of the joints of the hands.

**Case 5, an unmarried woman, aged 54 years,** was admitted to hospital on May 13, 1954. She complained of malaise of 2 weeks' duration with a generalized rash appearing on the body 8 days before admission. She had had recurrent conjunctivitis with pain in the eyes for 4 years with the typical sensation of grit in the eye. In January, 1954, she had had a moderate macrocytic normochromic anaemia. 25 years ago she had been treated for lupus erythematosus of the nose which had persisted subsequently without change. She had had, during the past year, occasional twinges of pain in the elbows, knees and thighs, and had had intermittent headache and vertigo.

Examination showed the skin of the nose pitted and purplish. There was a bilateral enlargement of the parotid glands. The skin of the lower leg showed a diffuse erythematous rash. There was a low grade pyrexia. The blood showed a slight anaemia and raised erythrocyte sedimentation rate. The skin specialist was of the opinion that there were lesions of the skin typical of acute lupus erythematosus.

**Case 6, a man, aged 49 years,** was seen at the outpatient department, complaining of dry gritty eyes with photophobia for 7 years. There was in addition a dry skin of the body mainly involving the arms and the legs. The tongue and mouth were dry in the morning.

In 1937 he had been treated in the Skin Department of the Edinburgh Royal Infirmary for lesions of the skin of the nose and arms which were confirmed by biopsy to be due to Boeck's sarcoidosis. A sister suffers from Raynaud's disease.

Clinical examination showed superficial scarring of the skin around the nose; the skin generally was fine and dry. There was moderate chronic bronchitis and emphysema. The conjunctivae were injected, Rose Bengal caused typical staining and Schirmer's test was positive.

In these last four cases the findings were much the same. There was a variable, but definite degree of normocytic hypochromic anaemia, save in Case 6 where the blood count was normal. The erythrocyte sedimentation rate was invariably raised. In Case 4 with scleroderma the serum globulin was normal and  $x$  rays showed arthritic changes in the hands. In the others the serum globulin was relatively raised as in Case 2. In Case 5, disseminated lupus erythematosus, there was a disturbance of liver function, and the tests showed thymol turbidity 38 McLagan units, and colloidal gold 653000. Examination of the blood in this case on two occasions failed to demonstrate any "L.E." cells. The other investigations in all cases gave results within normal limits.

### Comment

It is suggested that these cases are further evidence that this condition of kerato-conjunctivitis sicca occurs in association with a variety of conditions of probable inter-related aetiology and pathology and that Sjögren's syndrome is one of such associations. The occurrence of kerato-conjunctivitis sicca with polyarteritis nodosa has been noted by Cardell and Gurling (1954) and with a case of disseminated lupus erythematosus by Morgan (1954). MacLean and Robinson (1954) described a case of the syndrome with L.E. cells present in the blood.

Sjögren (1933) corroborated and augmented the findings of several physicians to crystallize the syndrome bearing his name. The condition is almost, but not quite exclusively found in women of middle-age and over and is of gradual onset. The essential lesion of the eye is the lack of tears and the protection given by them to the delicate epithelium of the con-

conjunctiva and cornea. The areas of cornea and conjunctiva exposed when the eyelids are open, suffer and unlike normal epithelium they stain with a solution of Rose Bengal. Sjögren considers this pathognomonic. Schirmer's test is a quantitative method of measuring the production of tears by absorbing the amount produced on a strip of filter paper. The syndrome is characteristically accompanied by a polyarthritis of rheumatoid type in two-thirds of the cases.

It has been recognized recently that the conditions of acroscleroderma, periarteritis nodosa, and disseminated lupus erythematosus probably belong to a group of diseases affecting collagen tissue, and that these collagen diseases include rheumatoid arthritis, rheumatic fever, and dermatomyositis (Banks, 1941; Klemperer, Pollack, and Baehr, 1942). The aetiological features cited in Sjögren's syndrome and the above conditions are very similar. With regard to periarteritis nodosa, Klotz (1917) suggested a streptococcal invasion. Harris and Friedrichs (1922) thought a virus might be responsible. Allergy has been incriminated (Ophuls, 1923). Endocrine dysfunction (Selye, Sylvester, Hall, and Leblond, 1944) and sensitization to various substances, mainly serums and sulphonamides (Rich, 1942; Rich and Gregory, 1943), have been mentioned.

Similar aetiological conditions have been related to disseminated lupus erythematosus (Baehr, Klemperer, and Schiffrin, 1935; Klemperer and others, 1942; Fox, 1943).

Acroscleroderma, the condition of close association of scleroderma with Raynaud's phenomenon, results in appearances described in Case 4 (Hutchinson, 1896). The aetiology has been discussed along similar lines to the above by Lewis (1938), Mayo and Adson (1932), Prinzmetal (1936), and Sodeman and Burch (1939).

The pathology of these conditions has also been given comparatively common ground. The primary lesion with involvement of the collagen tissue of the blood vessels is well known in periarteritis nodosa and disseminated lupus erythematosus (Harris, Lynch, and O'Hare, 1939; Banks, 1941; Klemperer and others, 1942; Miller and Daley, 1946). In acroscleroderma, Prinzmetal (1936) and later Sodeman and Burch (1939) concluded that it was likely that some change of unknown origin in the collagenous part of the skin and subcutaneous tissue was involved in the production of scleroderma.

The aetiology of "Boeck's" sarcoidosis remains a riddle. It has been critically discussed by Middleton (1954), who examined the evidence which has accumulated regarding its relationship to many conditions, which include tuberculosis, brucellosis and leprosy, fungus infections, histoplasmosis and toxoplasmosis, nematode infestation, leishmaniasis, and reactions to talc, silica dioxide, and beryllium phosphors. He concluded that it is a clinical entity and that none of these relationships is of consequence. Keratoconjunctivitis sicca was seen in the last case with cutaneous sarcoidosis.

To discuss the aetiology of Sjögren's syndrome is simply to reiterate the aetiological features mentioned above. There has been a recent review by Duke-Elder (1952). The modern treatment of all these conditions has included cortisone and ACTH among specific measures. The results have been variable, but some cases of polyarteritis nodosa, disseminated lupus erythematosus, and acroscleroderma have shown remissions of variable intensity and duration (Irons, Ayer, Brown, and Armstrong, 1951; Baggenstoss, Shick, and Polley, 1951; Brunsting, Slocumb, and Didcoct, 1951; Kierland and Hines, 1951). Local treatment to the eye with cortisone has proved on the whole of little value, and systemic treatment of the related condition has had no apparent effect on the conjunctival involvement.

### Summary

Six cases of kerato-conjunctivitis sicca are briefly described. There was related parotid gland enlargement in some; in association in two cases there was rheumatoid arthritis (Sjögren's syndrome); in the other cases there were separately, polyarteritis nodosa, disseminated lupus erythematosus, acroscleroderma, and Boeck's sarcoidosis. The aetiology is discussed.

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