POLYARTERITIS NODOSA*†
WITH AN UNUSUAL OCULAR PRESENTATION

BY

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POLYARTERITIS nodosa (periarteritis nodosa), first described by Kussmaul and Maier (1866), is a relatively rare disease, but considerable attention has been paid to it in recent years.

Duke-Elder (1962), describing the condition, wrote: "this is a disseminated disease of obscure cause characterized by necrosing oblitative lesions of small arteries and arterioles which appear nodular owing to the formation of aneurysms or granulomatous proliferation". Harvey (1963) described the lesions as segmental in their distribution and involving arteries throughout most of the body so that the resulting clinical picture was one of polymorphic manifestations which might seem unrelated. In its typical form, polyarteritis nodosa is a well-defined entity, but is not always typical (Anderson, 1961).

This case of polyarteritis nodosa with an unusual ocular presentation is reported in full detail because it demonstrates the difficulty in diagnosis of the underlying condition with such a presentation. Harbert and McPherson (1947) described a similar case, but the lacrimal gland was not involved. Cogan (1955) reviewed and reported cases of corneoscleritis or scleritis associated with polyarteritis nodosa, and Moore and Sevel (1966) have recently reviewed cases associated with either polyarteritis nodosa or Wegener's granulomatosis, in none of which the lacrimal gland appeared to be affected. Dacryoadenopathy does not appear to have been reported as a presenting symptom in polyarteritis nodosa.

Case Report

A man aged 60 years first attended the Nottingham Eye Hospital on December 18, 1964, complaining of a swelling of the outer part of the right upper eyelid of 4 weeks' duration, and a red sore right eye for about 6 weeks. There was also a 5-week history of an upper respiratory tract infection which had been slow to settle with tablets oxytetracycline 250 mg. four times a day given by the general practitioner. The patient was also attending the E.N.T. Department for "indrawn eardrums", and was treated for eustachian catarrh with some residual bilateral deafness.

History.—There had been recurrent attacks of bronchitis in 1921, 1922, 1924 (Jan.), 1924 (Nov.), 1925, 1929, 1930, and 1947, for which the usual treatment appears to have been Mist. Expect. In 1953, the patient had been treated with aspirin and liniment for rheumatoid arthritis of the wrists and fingers. There were upper respiratory tract infections in 1954, 1960, 1963, and Nov. 1964, but only for the last attack had systemic antibiotics been given. At no time were sulphonamides recorded as having been given.

On July 31, 1954, the blood pressure was recorded as 165/85. In March, 1964, there had been a complaint of pain in the legs when walking, but no abnormality or underlying cause was found.

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Examination.—The visual acuity was 6/9 in each eye. A slight swelling was present in the region of the right lacrimal gland. There was a mild generalized conjunctivitis, with a small area of nodular episcleritis and superficial punctate keratitis in the right eye. The left eye was white and quiet. The intra-ocular pressures, fundi, and discs were normal.

Treatment.—Gutt. IDU 2-hourly and gutt. scopoline 0·1 per cent. three times a day to the right eye. Tabs. oxytetracycline 250 mg. four times a day were continued, and tabs. Becosym four times a day were added.

Out-patient Progress.—On December 29, 1964, the keratitis had improved but the swelling in the right lacrimal gland region had increased. This was diagnosed as a dacryoadenitis not sensitive to oxytetracycline, which was, therefore, changed to chlorotetracycline capsules, 250 mg. four times a day. After 2 weeks the swelling had resolved and the capsules and Becosym were discontinued. There was still some superficial punctate keratitis, and the drops were changed to oculentum Terramycin with polymyxin B.

X-rays of the skull, frontal sinuses, and antra showed no abnormality and there was no apical infection of the teeth. Chest X ray showed no focal lung lesion, but there were some chronic bronchitis changes.

On January 26, 1965, the nodular episcleritis, which had almost settled previously, had become more marked, but the keratitis was much improved.

Hospital Admission.—On February 12, 1965, 2 months after his first attendance, he complained for the first time of malaise with some nausea and vomiting. His right eye had again become painful and red, and the swelling of the lacrimal gland was much larger. The left eye was still white and quiet. He was admitted to the Eye Hospital for further investigation, and treatment was started with tabs. erythromycin 250 mg. four times a day.

Examination.—A general medical examination failed to show any clinical evidence of a neoplasm, and the chest was normal. Two teeth showed caries, but there was no infection or ulceration in the mouth. There was a mild pyrexia of 99·4°F. and the blood pressure was 160/70. The fundi were normal.

Laboratory Investigations.—Hb 12·4 g./100 ml. (84 per cent.); white blood count 10,000/c.mm. (neutrophils 6,100; eosinophils 900; lymphocytes 2,100; monocytes 400). Wassermann reaction and Kahn test negative. Erythrocyte sedimentation rate 110 mm. in 1 hour (Westergren). Total serum proteins 7·2 g./100 ml., with decreased albumin (3·1 g.) and increased globulin (4·1 g.). Three specimens of stool, taken on successive days, were all negative for occult blood. Urine showed only a trace of albumin.

Hospital Progress.—A week later, the pain, nausea, and vomiting had all settled, and the patient felt much better. His temperature, which had been between 99·2 and 99·4°F. during the week, was normal on the 8th day. The lacrimal gland swelling was still present.

After another week, the erythrocyte sedimentation rate had risen to 125 mm. in 1 hour and the white blood count was 9,000 (eosinophilia 630 per c.mm.). Rouleau formation in the blood raised the possibility of myelomatosis, but this was not confirmed. A bone marrow examination showed no evidence of leukaemia. X-ray of the dorsal lumbar spine showed no metastases, but there was narrowing of some of the discs and general osteo-arthritis. X-rays of the hands and pelvis showed no abnormality.

After a further week, he complained of some indigestion and the erythromycin was discontinued. The erythrocyte sedimentation rate had risen to 154 mm. and the white blood count to 12,500 per c.mm. (eosinophilia 500 per c.mm.). Total serum proteins 7·0 g./100 ml. (albumin 2·8 g., globulin 4·2 g.). Hb was only 7·1 g./100 ml. (49 per cent.) and a transfusion of two pints of blood was therefore given.

Biopsy.—A specimen from the right lacrimal gland region was taken on March 12, 1965, and sent to Prof. Norman Ashton, Department of Pathology, Institute of Ophthalmology, London, who reported as follows:

Sections of the biopsy taken from the region of the right lacrimal gland showed no glandular tissue. The specimen consisted of a mass of fibro-fatty tissue containing within it numerous blood vessels showing intense subacute perivascular inflammatory reaction in which eosinophils were a predominant feature. A few giant cells were present (Figs 1 and 2, opposite).
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Fig. 1.—Biopsy from region of lacrimal gland, showing fibro-fatty tissue containing numerous blood vessels. ×73.

Fig. 2.—High-power view of Fig. 1. The blood vessels show intense subacute perivascular inflammatory reaction. A few giant cells are present (eosinophils are a prominent feature although not demonstrated in the black and white picture). ×115.

There was no evidence of a neoplasm, and the histological picture was highly suggestive of periarteritis nodosa or some other form of nodular vasculitis, which would fit in well with the patient's clinical condition.

Further Progress.—A few days later the patient complained of nausea and abdominal pain, and, within a few hours, passed slightly blood-stained urine. The following day, the haematuria was more marked.

The next day (4 weeks after admission) he complained of severe abdominal pain, and had gross haematuria, albuminuria, occult blood in the faeces, a slight haemoptysis, and an epistaxis. Blood urea 560 mg./100 ml.; Hb 10.1 g./100 ml. (69 per cent.); white blood count 14,000 per c.mm. (eosinophilia 280 per c.mm.). The patient was transferred to a medical ward.

Progress in Medical Ward.—His general condition was noted to be poor, and he was uremic, but the only abnormal finding was the nodular episcleritis. The keratitis had cleared, and there was no lacrimal gland swelling following the biopsy.

Blood pressure 160/90; erythrocyte sedimentation rate 132 mm. in 1 hour. The serum potassium was raised (6·9 mEq./litre). He was started on restricted fluids. Next day (March 20, 1965) the blood urea had risen to 600 mg./100 ml., and the urine output was diminished, with gross haematuria. On March 21, 1965, the blood urea was 640 mg./100 ml. and the serum potassium 6·8 mEq./litre. The patient was now anuric. The blood urea and serum potassium readings were 700 and 840 mg./100 ml. and 7·4 and 8·2 mEq./litre on the following two days.

Termination.—On March 24, 1965, the patient lapsed into coma, and he died the next day, 6 weeks after admission to hospital, 14 weeks after he was first seen, and 5 months after the onset of symptoms.

Post Mortem Findings

(Report by Dr. G. F. M. Hall, Pathology Department, Nottingham General Hospital)

Macroscopic Appearances.—There were scanty adhesions of the pleurae at the right apex. The bronchi contained scanty mucopus and there was severe generalized oedema of the lungs. The heart, weighing 410 g., showed slight left ventricular hypertrophy.

The gastrointestinal tract appeared normal, but was not opened up in its entirety. Both the outer and the cut surfaces of the spleen were speckled with tiny white raised foci, rather like tubercles, some of which were confluent.
The kidneys were enlarged (right 225 g., left 280 g.) and the cut surfaces showed the cortex to be disorganized by innumerable tiny white foci, most of which were confluent forming a network. Discrete white foci were also present in smaller numbers in the medulla.

The under surfaces of the frontal and temporal lobes of the brain showed foci of haemorrhagic speckling. The tissue from the corner of the right orbit was excised and formed a flattened pyramidal mass of firm white tissue 2 cm. in maximum extent.

Histology.—The kidneys showed a diffuse necrotizing glomerulonephritis, with hardly any normal glomeruli (Fig. 3). In a typical lesion (Fig. 4), the glomerulus which was almost destroyed consisted of a central distorted focus of fibrinoid necrosis surrounded by inflammatory infiltration composed mainly of neutrophil polymorphs, with less numerous plasma cells and lymphocytes, and scanty eosinophils. There were also occasional fibrotic or partially fibrotic glomeruli, and these showed less intense inflammatory infiltration. Many of the tubules were destroyed by these inflammatory granulomatous foci, which were also found less frequently in the medulla, some orientated around capillaries, but others centred on tubules. There was acute fibrinoid necrosis of most of the central arterioles of the spleen, frequently spreading out into irregular fluffy exudate surrounded by predominantly polymorphonuclear infiltration with occasional eosinophils (Fig. 5, opposite). The liver showed an occasional granulomatous focus in the portal tracts, but no vascular lesions were evident.

Oedema only was present in the lungs, no granulomatous or vascular lesions being found in the random block examined. The basal area of the brain showed acute angiitis, with fibrinoid necrosis, extravasation of red cells, and surrounding polymorph infiltration, involving small meningeal vessels, both arterioles and venules. Mild diffuse meningeal infiltration with lymphocytes, plasma cells, polymorphs, and macrophages was also present (Figs 6 and 7).

Lacrimal tissue was readily recognized in the specimen from the right orbit, but there were varying degrees of atrophy, fibrosis, and infiltration with lymphocytes and plasma cells. There were also occasional circumscribed granulomatous foci, including scanty polymorphs, but vascular lesions were no longer evident in the residual tissue.

Comment.—The overall picture was not that of classical polyarteritis nodosa, although it was evidently a related condition which could be included under the general heading of "necrotizing angiitis". It fits best with that type described by Allen (1962) as acute allergic angiitis. Many such
cases appear to be due to drug allergy, but this cannot be established in all cases, although the histological reaction suggests a hypersensitivity reaction.

**Pathological Diagnosis.**—Uraemia, acute necrotizing glomerulonephritis, acute disseminated angitis, and right dacryoadenitis.

**Discussion**

Wise (1952), in discussing ocular involvement in polyarteritis nodosa, wrote that it has been reported to occur in ten to twenty per cent. of cases, and from a review of the literature, he listed 24 ocular symptoms, dividing them into the frequent and the rare (the latter including corneoscleritis). However, cases of polyarteritis nodosa which first present with ocular symptoms are rare and Boyd (1940) found only one in a hundred cases.
According to Duke-Elder (1965a), the collagen diseases all involve the lacrimal gland and are commonly associated with the development of keratoconjunctivitis sicca in varying degrees. This is well demonstrated by the biopsy and post mortem specimens of the lacrimal gland, showing varying degrees of atrophy and fibrosis. He was also of the opinion (Duke-Elder, 1965b) that a hyperaemic conjunctivitis may be the only complication. The corneal complications, however, are more common and serious. These may be limited to the cornea itself as a superficial oedema with scattered punctate epithelial lesions, but more usually the sclera is involved as well.

The precise aetiology of polyarteritis nodosa is still unknown, but various factors have been suggested. Gruber (1925) stated that this disease might represent a reaction evoked by various infections, allergic or toxic agents. This theory received support from cases of serum sickness (Clark and Kaplan, 1937; Rich, 1942) and from numerous animal experiments, such as those of Rich and Gregory (1943). Arkin (1930) believed a specific infection to be present, probably caused by a filterable virus.

Rose and Spencer (1957) have presented evidence that abnormal immune reactions to respiratory infections may be the basis for polyarteritis nodosa, and Harvey (1963) said that many patients who acquire this disease are already suffering from a chronic or recent acute respiratory infection. In the present case an upper respiratory tract infection developed almost simultaneously with the eye symptoms, and there was a long history of eleven similar attacks and attacks of bronchitis going back to 1921. It seems possible, therefore, that all these attacks were a factor in the aetiology.

Hollenhorst and Henderson (1951) are of the opinion that polyarteritis nodosa is always part of a hypersensitivity reaction, characterized by an abnormal response of the mesenchymal derivatives to an antigen. Goldberger (1959) believed the mechanism to be an antigen—antibody reaction damaging the vessel wall and also the kidney. The arteritis so produced leads to a decreased circulating blood volume, which, with kidney injury, leads to aldosterone secretion and so to a further intra-arterial oedema and necrosis and, finally, to the establishment of persistent polyarteritis.

Zeek (1952), using the generic term necrotizing angiitis, recognized five groups which she believed were morphologically and clinically distinct, but admitted that cases occurred which could not be rigidly classified. Her two groups relevant to this case are periarteritis nodosa and hypersensitivity angiitis. Allen (1962), describing the latter condition, wrote that focal necrotizing glomerulonephritis was a frequent and often fatal accompaniment. The condition was found in this case and is well demonstrated in Figs 3 and 4. The spleen shows acute fibrinoid necrosis with surrounding polymorphonuclear inflammatory infiltration with occasional eosinophils (Fig. 5) but, unlike Allen’s description, there was no evidence of any necrotizing angiitis in the lungs.

The onset of polyarteritis nodosa has frequently been observed after the administration of numerous therapeutic agents, such as thiouracil (Gibson and Quinlan, 1945), iodine (Rich, 1945), phenylbutazone (Hodge and Lawrence, 1957), sulphonamides (French, 1946; Lichtenstein and Fox, 1946), penicillin (Waugh, 1952), chloramphenicol (Rose and Spencer, 1957), and streptomycin (Edge, Fazlullah and Ward, 1955). A hypersensitivity reaction, in the form of classical polyarteritis nodosa or of generalized hypersensitivity angiitis, does not appear to have been described after the administration of tetracyclines. Indeed, Symmers (1962) concluded that “the role of drug allergy in the aetiology of any case of any of the ‘collagen diseases’ is far from having been established”.

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The tetracyclines are known to have certain toxic side-reactions (Goodman and Gilman, 1965) and one of these, an adult-type acquired Fanconi syndrome, has been reported by Zimmerman and Werther (1964) who also discussed several cases reported by other authors, and more recently by Fulop and Drapkin (1965). These cases have usually followed the ingestion of “outdated” batches of tetracycline which have been exposed to conditions of heat and moisture during storage. The presence of citric acid in the formulation allows the development of a high pH and the formation of anhydrotetracycline and epianhydrotetracycline which are toxic degradation products. To exclude such toxic effects in this case, a careful check was made of all the tetracyclines used, and none contained citric acid (Haydock, 1965, 1966).

Lepper, Wolfe, Zimmerman, Caldwell, Spies, and Dowling (1951) first observed that the tetracyclines might damage the liver, and Sborov and Sutherland (1951) reported that patients receiving large oral doses of tetracyclines developed clinical evidence of hepatic dysfunction. Temporary deterioration in renal function has been reported in patients with a pre-existing significant renal impairment causing retention of the drug (Shils, 1962, 1963). Málek, Zástava, Zák, Kočvara, and Kolc (1963), using a fluorescence technique, found that a tetracycline complex formed in pathologically altered tissues which had quite different properties and remained in them for days or weeks. Thus, in this patient, the underlying pathology would cause retention in the tissues and the blood, giving rise to much higher blood levels and probably further tissue damage.

Allen (1962) concluded that “all of the clinical as well as the morphological features of hypersensitivity angiitis, allergic granulomatous angiitis, and periarteritis nodosa may occur in an individual case as if dependent on the concentration of the allergen and the reactivity of the host”.

The tetracyclines given for the original symptoms, which, in retrospect, were manifestations of the polyarteritis nodosa, are unlikely to have caused the disease. However, it is probable that a hypersensitivity reaction and toxic reactions due to greater retention of the tetracyclines in the tissues were factors in accelerating the course of the disease.

Summary

A case of polyarteritis nodosa, which presented with the unusual ocular complication of dacryoadenopathy, is described in detail. The aetiology is discussed, particular reference being made to the tetracyclines and their possible role in lesions of this type.

Pathological support for the diagnosis is given by a report of the general post mortem findings and the biopsy, and is demonstrated in the photomicrographs.

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