WEGENER'S GRANULOMATOSIS

Granuloma of the nose with systemic polyarteritis nodosa

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Rose (1956), in an investigation of 66 cases of polyarteritis nodosa without lung involvement, found a preceding history of upper respiratory infection in 12 cases, i.e. 18 per cent. It may well be that infection rather than any drug used for its suppression may give rise to a state of hypersensitivity with the production of systemic polyarteritis. There is much to support such a hypothesis from consideration of a particular group of cases of polyarteritis originally described by Klinger (1931) and Wegener (1937, 1939). These cases are characterized by symptoms and signs of respiratory tract infection with the formation of granulomata and later by the development of polyarteritis, progressive renal involvement and death from uraemia.

Since the original descriptions some 25 additional cases have been reported. Many of these reports are concerned with the pathological features for the very obvious reason that the diagnosis has, in the past, often been a post-mortem one. However, with increasing accuracy of recognition, the problems of diagnosis and treatment are assuming a position of more importance. The variety of physical signs which may appear are of considerable interest and the following case illustrates some of the more unusual features of Wegener's granulomatosis.

Case Report

Presenting Features

An Irish girl, aged 19 years, was admitted to hospital on August 20, 1955, with a complaint of one month's sweating, fever and headache. For two days she had also been vomiting. One week before admission she had attended another hospital because of a small crusted skin lesion which had appeared on the right temple. There was no significant past or family history.

Physical examination revealed a pale, ill-looking girl with a puffy face and a slight saddle deformity of the nose (Fig. 1). On the right temple there was

FIG. 1.—The exophthalmos is now bilateral and more marked on the right, where there is considerable chemosis. The face has become far more puffy and the nasal deformity is more marked (before cortisone).

a small crusted area. She ran an intermittent pyrexia up to 100.6°F. There were, at that time, no other physical signs. The blood pressure was 140/80 mm. Hg.

Investigations

X-ray film of chest—no abnormality. Blood

picture—haemoglobin 13.2 g. per 100 ml. (89 per cent.); white blood cells, 6,900 per cu mm.; normal differential count; Wassermann reaction (blood) negative. Blood cultures sterile on several occasions. Blood urea, 20 mg. per 100 ml. Catheter specimen of urine—red blood cells, granular casts and albuminuria. Plasma proteins—normal total and differential levels. Bone marrow—no abnormality. Lumbar puncture—chemically and cytologically normal fluid under normal pressure. Cultures of nasal swabs produced a growth of *staph. pyogenes* sensitive to tetracycline and streptomycin.

The only abnormality appeared to be microscopic haematuria and cylinduria, which were consistently present.

Nasal Discharge and Exophthalmos

A month after admission the patient had several epistaxes and admitted that she had noticed a nasal discharge and heavy nasal catarrh for the past three months. X-ray examination of the nasal sinuses showed evidence of chronic nasal obstruction with fluid levels in both maxillary sinuses. She also began to develop slight exophthalmos, at first affecting the right eye alone, but later bilateral and progressive, with considerable chemosis, periorbital oedema and some patches of scleritis developing (Fig. 1). An ulcer also appeared on the hard palate, accompanied by increasing saddle deformity of the nose.

Biopsy

Specimens were taken from the palatal ulcer, the skin lesion and the nasal mucosa, examination of the nose having revealed evidence of nasal sepsis with considerable crusting of the mucous membrane.

1. *Right temple.* The epidermis was ulcerated, the floor of the ulcer being lined by fibroblastic granulation tissue infiltrated by lymphocytes, eosinophils and plasma cells. The granuloma became more extensive in the deeper layers of the cutis, where a central area of eosinophilic necrosis was surrounded by numerous giant cells, some of the foreign body and some of the Langhans type. This inflammatory tissue extended into the subcutaneous fat.

Several arteries in the subcutis were involved by the granuloma, all the coats were affected and the lumen was filled with granulomatous tissue (Fig. 2), including giant cells. Elastic staining showed splitting and partial disappearance of the elastica interna (Weigert and van Gieson). Fibrinoid changes were not seen (phosphotungstic acid haematoxylin).

2. *Right middle turbinate.* The mucosa was

FIG. 2.—Right temple: (a) arteritis affecting all coats. The lumen is filled with granulation tissue. H. & E. $\times 150$.

ulcerated with conspicuous submucous oedema. More deeply there was an infiltration by neutrophils, eosinophils and plasma cells; the neutrophils invaded the media of several small submucous arterioles. Centrally there was fibroblastic granulation tissue with giant cells, similar to that seen in the temple. Necrosis was not seen. Vascular lesions were confined to small arterioles and did not affect larger vessels.

3. *Palate.* The mucosal epithelium was partly ulcerated; where present, it was thickened with peg-like prolongations into the stroma. The stroma was mostly replaced by blood clot, pus and granulation tissue containing many giant cells, some of the foreign body and some of the Langhans type. A blood vessel, probably a vein, with its media heavily infiltrated by neutrophils, was surrounded by many giant cells. Fibrinoid change was not seen.

Ziehl-Neelsen preparations were negative for acid-fast bacilli in all sections.

The histological diagnosis was malignant granuloma of the nose.

FIG. 2.—(b) The elastic lamina is interrupted, and shows splitting. Weigert-van-Gieson $\times 150$.

Progress and Further Investigations

The exophthalmos gradually progressed, the nasal sepsis continued, and the urine persistently contained a deposit of red blood cells, pus cells and casts. Examination of the serum proteins by electrophoresis now revealed reversal of the albumin-globulin ratio with an increased proportion of gamma-globulin. There was also increasing nitrogen retention (blood urea 90 mg. per cent.); persistent anaemia had developed (haemoglobin 60 per cent.), as had moderate hypertension (160/100 mm. Hg.).

Suspicion of Wegener's granulomatosis led to biopsy of a specimen of muscle from the right thigh (Mr. J. B. Hobbs).

Histology of Muscle Biopsy

Several small arteries showed an acute inflammation (Fig. 3), the adventitia and media being infiltrated by plasma cells, lymphocytes and polymorpho-nuclears, among which eosinophils were conspicuous. The media showed fibrinoid necrosis. There was some intimal proliferation. Elastic staining showed in one vessel a complete destruction of the elastica interna.

In other vessels there was an obliterative endarteritis, the affected vessels being surrounded by a moderate amount of haemosiderin pigment. The lumina of these vessels contained a cellular fibroblastic tissue in which capillary recanalization was seen (Fig. 4); the media and adventitia showed a scanty infiltration by neutrophils and eosinophils and occasional granules of haemosiderin were present in these layers.

There was moderate increase in inter-fascicular nuclei with occasional lymphocytic collections. A patchy degeneration of muscle was seen, the fibres being swollen with loss of staining reaction and striation.

The combined evidence of acute allergic arteritis of the polyarteritis nodosa type and of a granulomatous process in the nose confirmed the clinical diagnosis of Wegener's granulomatosis.

Treatment

Cortisone. Dramatic improvement of the chemosis and exophthalmos followed cortisone therapy alone, and this has been a most notable feature throughout. Temporary cessation of hormone therapy always led to recurrence of the exophthalmos, which again improved with further cortisone. The palatal ulcer also healed with this therapy and there was no further vomiting.

The patient's pyrexia, however, was not completely controlled. She was greatly distressed by a copious and foul nasal discharge and by the alarming alteration in her face.

Unfortunately, large doses of cortisone soon induced a paranoid psychosis which necessitated termination of therapy.

Local X-ray Treatment. As withdrawal of cortisone was followed by a return of pyrexia, vomiting and a worsening of the ocular manifestations, it was decided to try a course of local X-ray therapy. This produced a temporary improvement in well-being, but the original exophthalmos soon returned.

In January 1956 the patient took her own discharge, only to be readmitted three weeks later with a return of her symptoms and gross bilateral exophthalmos.

Combined Cortisone and Antibiotics. Treatment was recommenced with cortisone, 100 mg. daily by mouth, and antibiotics in the form of tetracycline, 500 mg. q.d.s. Since this time there has been an improvement in the patient's symptoms: the nasal discharge has decreased, the pyrexia and vomiting have ceased and the exophthalmos is now non-progressive. The palatal ulcer has remained healed and the degree of nitrogen retention has decreased (blood urea 41 mg. per 100 ml.).

Discussion

The condition of systemic polyarteritis associated with chronic sepsis and granuloma formation in the respiratory tract is rare. Affecting both sexes, it is usually most common in the fourth or fifth decades, although the age of onset has varied from 12 years (Godman and Churg, 1954) to 70 years (Ahlström *et al.*, 1953) in the cases recorded. Few of these cases have been reported in this country.

Almost any portion of the respiratory tract can be affected by the process of granuloma formation. Lesions are commonly found in the nose and accessory sinuses, also in the pharynx and larynx, and in other cases granuloma formation has occurred in the lung parenchyma. Sometimes lesions are found in both situations.

Criteria for Diagnosis

Godman and Churg (1954) give three criteria for the diagnosis of Wegener's granulomatosis: (1) necrotizing granuloma of the upper and/or lower respiratory tract; (2) generalized focal necrotizing vasculitis; and (3) glomerulonephritis. In our case the first two of these criteria have been established. The presence of glomerulonephritis is adduced by the persistence of haematuria and the slow rise in the blood urea.

Taken separately, the lesions of the nose and palate in this case conform with descriptions of 'malignant granuloma' or granuloma gangraenescens of the upper respiratory tract (Ellis, 1955). The lesion on the temple in our patient may be an extension from an underlying involved nasal sinus or a cutaneous granuloma. The granulomata of specific infections, such as tuberculosis and brucellosis, were at first suspected as the cause of the temporal lesion, but the nasal symptoms revealed the true nature of the condition and no specific organisms could be demonstrated either bacteriologically or histologically.

The generalized vasculitis found in Wegener's granulomatosis may be 'hypersensitivity angiitis,' described by Zeek *et al.* (1948), or polyarteritis nodosa. In our case the generalized lesion is considered to be polyarteritis nodosa, despite the absence of symptoms, because muscular arteries and not veins are involved, and healing processes, usually absent in hypersensitivity angiitis, are prominent (recanalization of occluded arteries and haemosiderin deposition). The lesions of the nose and temple accord more with the appearance of hypersensitivity angiitis in that veins are involved, although the presence of granulomata in the lumina of arteries suggests the beginnings of healing following thrombosis. It should be noted that muscle biopsy may be negative, though the condition is suspected clinically (McCallum, 1954).

FIG. 3.—Muscle: acute arteritis with fibrinoid necrosis of media. H. & E. $\times 300$.

Pathogenesis

For the pathogenesis of the condition Williams (1949) and Godman and Churg (1954) postulate the following train of events: infection of the respiratory tract, hypersensitivity with granuloma formation developing in this easily sensitized locus. Later, generalized hypersensitivity occurs, with vasculitis and glomerulonephritis. In our case constitutional symptoms were present only one month after nasal symptoms, and haematuria and albuminuria were present at the first examination, so that it is probable that generalized vasculitis and glomerulonephritis developed soon after, if not concomitantly with, the nasal granuloma. Pagel (1951, Case 3) has shown that tuberculoid giant cell granulomata involving blood vessels may, in fact, occur in polyarteritis nodosa. It seems, then, that the nasal granulomata and the generalized and renal lesions of Wegener's syndrome may all be slightly differing expressions of a single pathological process—in our case polyarteritis nodosa (Klinger, 1931). It may be that the polyarteritis is an expression of hypersensitivity to the chronic antral infection, but it is also possible that the generalized hypersensitivity, resulting from un-

FIG. 4.—Muscle: healing arteritis showing capillary recanalization of granulation tissue filling the lumen. H. & E. $\times 300$.

known causes, first manifested itself in this obvious site while remaining latent elsewhere till exacerbation and further investigation revealed the full extent of the disease.

Clinical Picture

The process of chronic sustained sepsis in the upper respiratory tract commonly manifests itself by the appearance of a purulent nasal discharge and X-ray evidence of sinus infection. Progressive destruction of the nasal cartilage may result in a saddle nose deformity (Wegener, 1936; Lindsay *et al.*, 1944), and this, combined with evidence of palatal involvement and ulceration, as has occurred in our case, may lead to a not unjustifiable diagnosis of syphilis. Involvement of other structures closely associated with the nasal sinuses may result in lesions in the middle ear (Johnson, 1948) and in the orbit giving rise to exophthalmos (Klinger, 1931; Stratton *et al.*, 1953; Howells, 1955).

In the present case exophthalmos, although commencing as a unilateral lesion, has progressed so that both eyes are affected. Bilateral exophthalmos produced in this way has only been reported on one previous occasion (Klinger, 1931), and then this was merely a terminal event. The presence of bilateral exophthalmos may lead to further pitfalls in diagnosis.

The cause of the progressive bilateral exophthalmos is of great interest. In the two cases recorded by Friedmann (1955), where unilateral exophthalmos occurred, clearance of the orbit was employed as a means of therapy and thus afforded the pathologist an opportunity for examination of

the orbital tissues. Here it was found that the exophthalmos was associated with the presence of granulomata in the orbit behind the affected eye. In our case this may perhaps also be the answer, but it is difficult to imagine that cortisone could make such a dramatic change if it merely did so by inhibiting the growth of the orbital granuloma. Another possibility may be that the cortisone decreases the inflammatory oedema in the retro-orbital tissues, giving rise to a recession of the eye. The presence of myositis—swelling and loss of striation of fibres and increase in nuclei (probably ischaemic changes secondary to arteritis)—of the thigh muscles may point to an additional cause for the exophthalmos: similar lesions of the ocular muscles may lead to an increase in their size and this may partly or wholly account for the exophthalmos and would also account for the external ophthalmoplegia which was a notable feature.

The condition of 'malignant granuloma' known to the otorhinolaryngologist may also readily be confused with Wegener's lesion. As pointed out by Friedmann (1955), external ulceration and death from necrosis and haemorrhage are not features of Wegener's granulomatosis, where external ulceration is rarely seen and death is usually caused by uraemia from renal involvement. Our case was, for many weeks, investigated as one of pyrexia of unknown aetiology, and it is worthy of note that an enquiry for symptoms of nasal infection was of great importance. Symptoms of this nature may not be readily volunteered by patients in a medical ward, as they are often considered by them to be of little importance.

Treatment

Treatment of this condition is difficult; few clinicians have been afforded an opportunity to treat cases because of their rarity. The therapeutic problems come under two main headings:

Control of respiratory sepsis. Respiratory sepsis seems to indicate a need for long-term antibiotic therapy supplemented by procedures such as antral drainage. Control of infection is of importance, not only because of the distressing complications associated with it, such as nasal deformity and copious nasal discharge, but also because the development of polyarteritis and its severity may be a direct consequence of this infection. However, the administration of antibiotics may lead to further sensitization and it is of note that in one case (Walton and Leggatt, 1956) the development of the syndrome has followed the use of streptomycin and PAS for the treatment of a granulomatous lesion wrongly suspected as being tuberculous. In all probability some product of infection is the cause of the hypersensitive state, but the classical experimental work of Rich and Gregory (1943) may serve as a reminder of the theoretical dangers of antibiotic administration.

Control of hypersensitive state. There seems no doubt that when antibiotics are used their administration should be covered by cortisone and there seems every reason to believe that antibiotics to combat the infective lesion plus cortisone to control the hypersensitive state is the most successful form of therapy for this condition. Godman and Churg (1954) record survival for 39 months on this combined therapy in one patient, whereas, with few exceptions, the disease usually runs a full course to a fatal outcome in untreated cases in six to 10 months.

In this case apparent control of pyrexia and of other symptoms with a marked recession of the eyes and a lessening of nasal sepsis seems to have been obtained by the joint use of these drugs. Cortisone used alone appeared to produce an incomplete response and, in the presence of uncontrolled infection, may, indeed, be dangerous. Similarly, X-ray therapy, although sometimes successful (Ellis, 1955) in cases of 'malignant granuloma,' would seem to play little part in the treatment of this syndrome.

One important feature throughout has been the

lack of symptoms referable to the systemic disease. It is perhaps worth remembering the presence of this condition when patients with chronic upper respiratory tract infection, which fails to respond to the usual therapy, develop unusual features either locally or outside the respiratory tract.

Summary

1. A case of Wegener's granulomatosis is described in which bilateral exophthalmos, palatal ulceration and progressive saddle deformity of the nose developed.
2. An important feature was the absence throughout the illness of symptoms and signs referable to the systemic disease, the diagnosis of which had to be confirmed by blind muscle biopsy.
3. The disease was controlled by combined antibiotic and cortisone treatment; neither of these was completely successful when given alone.
4. This condition should be remembered in all cases of chronic nasal infection which develop unusual features and do not respond to routine treatment.

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