Wegener’s granulomatosis: report of a patient surviving four and a half years

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SYNOPSIS A patient with Wegener's granulomatosis, treated with steroids on a long-term basis, survived at least four and a half years from onset until death occurred in an uncontrollable exacerbation of the disease process. This is believed to be the longest recorded survival.

Histological examination of the necropsy specimens suggests that the basic pathological lesion in this disease is the subendothelial deposition of so far unidentified material in the capillaries, arterioles, venules, and smaller arteries. The associated angiitis may be a consequence of this deposition. These vascular lesions are occlusive and adequately account for the observed infarctive changes. The granulomatous features of the disease probably represent a secondary reactive phenomenon.

The condition known as Wegener’s granulomatosis is characterized by the presence of necrotizing granulomata in the respiratory tract, focal necrotizing vasculitis and focal glomerulonephritis, usually terminating in uraemia (Tuhy, Maurice, and Niles, 1958). About 60 cases have so far been described, the average course of the disease being about five months (Walton, 1958) and the longest known survival four years (Fahey, Leonard, Churg, and Godman, 1954).

We report here the more protracted course of a case which finally came to necropsy; the histological findings can be interpreted as resulting from a single type of vascular lesion which can thus account for the diverse clinical features of this condition.

CASE REPORT

The patient, a factory worker, was 38 years old in October 1957 when he suffered a severe attack of sinusitis with photophobia. Three weeks later, he was admitted, stuporous, to the Department of Neurosurgery. A large right subdural haematoma and a small left subdural collection of blood were evacuated and he made a full recovery. He had sustained no head injury before this admission, during which right parotid swelling was noted.

Soon afterwards right peri-orbital swelling and proptosis developed. Needling of the para-nasal sinuses yielded no pus. Right-sided weakness and spasticity recurred and led to the removal of some left subdural granulation tissue in March 1958. He again made a complete recovery.

In September 1958 he complained of stiffness and swelling of the fingers and ankles. Small haemoptyses occurred and crops of painless, purpuric, maculopapules appeared on the legs and hands. The purpuric lesions tended to slough leaving behind shallow ulcers, several of which were to be seen on the hands, legs, buttocks, gums, and palate by the time of his re-admission in November. Chest radiographs showed discrete opacities in the right mid- and lower zones. Slight blood eosinophilia was present (640 per c.mm.). Other routine investigations were normal. A biopsy taken from the edge of a cutaneous ulcer showed a non-specific granulomatous reaction extending deeply into the dermis. The diagnosis of Wegener’s granulomatosis was made at this time and prednisolone therapy started. The response to treatment was most gratifying, the cutaneous, mucosal, and pulmonary lesions rapidly disappearing and full joint mobility being restored. Maintenance prednisolone therapy was continued and he worked regularly during the next two years.

In November 1960 he was again admitted with a 'pseudo-tumour' of the right orbit of some five weeks' duration. The orbital swelling and proptosis began to regress during a 14-day course of x-ray therapy and had entirely disappeared within two months. Chest radiographs during this admission revealed an opacity in the right lower zone with some pleural effusion.

During the succeeding 15 months he remained generally well. He reported recurrences of 'blood blisters' on the skin from time to time but these necrotic lesions and subjective stiffness in the fingers quickly cleared up when the dosage of prednisolone was temporarily increased.

In March 1962 he was admitted to hospital with haemoptysis and incipient gangrene of the left first, second, and third toes. The uvula was ulcerated and
his voice was reduced to a hoarse whisper. There was slight right spastic hemiparesis with right facial weakness of lower motor neurone type. All the peripheral arterial pulses were easily palpable and his blood pressure was 115/75 mm Hg. The only other clinical abnormalities were found in the right side of the chest. A radiograph showed two large opacities in the right mid- and lower zones, in one of which an air/fluid level was visible (Figs. 1 and 2). The E.S.R. was 31 mm in one hour (Wintrobe), haemoglobin 12·3 g./100 ml. (84%) with normal film appearances, and the urine contained a small amount of albumin although microscopical examination was normal. Renal function was normal.

Despite increased dosage of steroid, vasodilators and tetracycline therapy, the peripheral gangrene progressed. Mid-tarsal amputation of the left foot had to be carried out on 10 April, under steroid, penicillin, and streptomycin cover, and the wound proved slow to heal. Many of the small vessels in the amputation specimen were occluded by thrombus. Meanwhile the chest radiographic appearances remained unchanged. A two-week course of radiotherapy was given for the lung lesions but they had not changed significantly before rapid general deterioration set in a few days after skin-grafting of the amputation stump on 22 May. He became confused, developed persistent hiccoughs, and began to pass blood in the urine and bowel motions. He died on 4 June 1962.

POST-MORTEM EXAMINATION

At necropsy, superficial ragged ulcers were present in the lips, tongue, naso-pharynx, trachea and oesophagus, and throughout the alimentary tract. The lower lobe of the right lung contained circumscribed, indurated golden-yellow lesions showing a well-defined segmental distribution (Fig. 3). Within these lesions, white scar tissue of radiate distribution was present and in some such areas patent pulmonary vessels or bronchi were present. The rest of the lower lobe was hyperaemic and projected above the indurated mass. Of normal external appearance, the kidneys, in section, showed soft whitish lesions, up to 0·5 cm. in diameter, in the medulla.

HISTOLOGY

No lesions other than those observed macroscopically were found except for scant small inflammatory foci in the liver and a recanalized small artery in the peri-adrenal connective tissue.

RENAI LESIONS Glomerular lesions were widespread and of diverse appearance. The commonest change was irregular focal deposits of hyaline, poorly-eosinophilic material which did not show clear differential staining. In some glomeruli, this material appeared to be situated within the capillary lumen, but in several lesions these deposits were clearly sub-endothelial (Fig. 4). The plane of section of one
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FIG. 3. This shows the segmental nature of the pulmonary lesions. The darker peripheral areas are mostly necrotic tissue and the lighter-coloured areas, usually around patent bronchi or vessels, consist of hyaline scar tissue.

FIG. 4. The upper arrow indicates an area of amorphous subendothelial deposit which appears to distort the configuration of the capillary loop. At the lower arrow, the deposit is more uniformly distributed, less thick, and might be described as wire-looping. This material, however, does not stain with P.A.S. Haematoxylin and eosin × 450.

FIG. 5. Junction of an afferent arteriole and a glomerulus. The glomerulus is abnormal and contains irregular deposits which extend as a zone of darker staining along the intimal surface of the arteriole. The endothelial cells are desquamated. Haematoxylin and eosin × 250.
glomerulus included the afferent arteriole and this subendothelial deposit was seen to extend backwards along this arteriole (Fig. 5). Other glomerular changes included early capsular adhesions, fibrous crescent formation, and advanced sclerosis of some glomeruli. Complete glomerular infarction was common with some poorly staining glomeruli containing only a few pyknotic nuclei. In others, the capsule was filled with necrotic material and polymorphonuclear leucocytes. In such lesions there was no reaction outside the intact capsule. Some glomeruli showed haemorrhagic necrosis.

The macroscopic lesions were due to recent infarcts, and vascular lesions, of varied features, affected several intraparenchymal vessels, both arterial and venous. The least severe changes were evident in small arteries or arterioles with hyaline deposits in the inner part of the vessel wall altering the regular orientation of fibre. Other vessels showed complete disorganization with loss of elastic staining and dense infiltration of the walls with polymorphonuclears and lymphocytes. These lesions were similar to those illustrated by Symmers (1960) and affected arterial vessels between 150 μ and 600 μ in diameter. A few larger vessels were thrombosed and while some of these appeared to be veins, it was difficult to be sure because of the inflammatory destruction of the walls.

PULMONARY LESIONS  These lesions comprised areas of dense, hyaline fibrosis, areas of necrosis, diffuse interstitial fibrosis and pneumonitis in which there were dense aggregates of siderotic macrophages which probably accounted for the colour of the lesions. There was widespread bronchopneumonia and hyperaemic areas in the lower lobe comprised infarcted parenchyma in which some bronchopneumonic foci were still evident. The lung away from the localized induration in the lower lobe showed no evident effect of radiotherapy. None of the pulmonary changes was frankly granulomatous. A striking feature in the areas of fibrous scarring was the persistent patency of large pulmonary vessels, almost certainly arterial, in which there was complete hyaline fibrous replacement of the vessel wall, leaving no residual muscle or elastic structure. Within necrotic areas, stained for elastic, arterial outlines were still evident and in the areas of infarction many of the smaller arteries showed a gross exudative arteritis. A few smaller pulmonary arteries in the areas showing pneumonitis showed less severe arteritis.

ULCERATIVE LESIONS  The ulcers in the trachea and alimentary tract were generally shallow and those in the bowel were contained within the submucosa.

FIG. 6. A microscopic area of infarction of the tracheal mucosa in which the epithelial outline is still evident and which contains only scant inflammatory cells. Haematoxylin and eosin × 250.

The inflammatory exudate had no special features, comprising mainly lymphocytes and polymorphonuclears with no giant cell systems. The vessels near these lesions commonly showed severe inflammatory changes with the vessel walls densely infiltrated with polymorphonuclears. In several ulcers a striking feature was the presence of clearly discernible 'ghost outlines' of necrotic tissue in which there was no inflammatory exudate, this being confined to the margins of the infarcted areas (Fig. 6).

The aorta, femoral, popliteal, and tibial arteries were normal, as were the carotid and renal arteries.

COMMENT

Until the late stages of this disease process its exacerbations appeared to respond rapidly to temporarily increased steroid dosage. These short-term responses were so impressive as to suggest that maintenance steroid therapy may have exerted a favourable influence on some fundamental mechanism in this case, so contributing to the exceptionally
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long survival. The terminal phase, however, seemed quite unameliorated by heavy doses of steroids.

The kidneys showed scant chronic lesions and most of the glomerular lesions were acute. The typical glomerular lesions have previously been illustrated and described as fibrinoid necrosis but in this case were shown to be subendothelial deposits of an amorphous material. This process appears to have an occlusive effect, causing glomerular infarctive changes. A granulomatous reaction was not a feature of the renal lesions and the inflammatory changes in the infarcted glomeruli were confined within Bowman's capsule; while the extension of the granulomatous reaction outside the capsule has been described (Godman and Churg, 1954), this is probably a later phase of what is essentially an infarctive process. Renal lesions strikingly similar to those we describe here have recently been found in association with pulmonary haemosiderosis (Saltzman, West, and Chomet, 1962).

In the lungs the hyaline fibrous replacement of the vessel wall is probably a unique finding. Symmers (1960) described the walls of pulmonary vessels as sometimes breached by segmental fibrous scars. This type of lesion seems to be explicable only on the basis of angitis, with subsequent ischaemia and fibrosis, affecting the vasa vasorum of pulmonary arteries large enough to incorporate arterioles as vasa vasorum. The other pulmonary lesions are also explicable on the basis of regional occlusive angitis affecting arteries of the order of size 150 to 600 μ.

Granulomatous lesions were confined to the upper respiratory tract and the alimentary tract. The central areas of necrosis which were free from inflammatory exudate strongly indicate that the surrounding granulomatous or exudative lesions were secondary and reactive changes to occlusive vascular disease which in these areas comprised an inflammatory infiltration and destruction of the vessel wall. Such severe changes in the arteries in the kidney were uncommon and confined to infarcted areas.

The relation of the subendothelial lesions of the capillaries, arterioles, and small arteries to the exudative arteritis is difficult to define, but in some renal arteries hyaline deposits in the wall were present with a fairly scant inflammatory infiltration and it seems likely that the subendothelial deposits are the earliest phase, with subsequent development of an exudative arteritis.

From such considerations it appears that Wegener's granulomatosis is primarily an occlusive vascular disease which in the kidney affects glomerular capillaries and in other parts of the body shows regional involvement of arterioles and small arteries. The granulomatous element in the disease appears to be secondary to infarctive necrosis. The comparative lack of frankly granulomatous reaction in the case we describe may merely reflect the chronicity of the respiratory tract lesions or may be a consequence of the treatment given.

We are grateful to Dr. O. Brenner and Mr. J. M. Small for permission to publish details of this case, and to Messrs. T. F. Dee and S. A. Gaunt for help in preparation of the figures.

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doi: 10.1136/jcp.16.3.215

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