GOODPASTURE'S SYNDROME

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Despite the protean clinical manifestations of nephritis[1] and the multitude of classifications dealing with this disease, several specific and distinctive entities have been identified in recent years. One of these is Goodpasture's syndrome. The first description of this disorder is attributed to Goodpasture,[2] whose name Stanton and Jange[3] applied to the association of haemoptysis with later pulmonary infiltration, severe anaemia, renal failure, azotaemia and a short fatal course. It was not until 1955 that case reports of this syndrome became more prevalent. Since then some 53 case reports have appeared indicating a world-wide distribution: Australia,[3] England,[4-9] Germany,[10] Ireland,[11] New Zealand,[12] Norway,[13] the United States[2,14-22] and South Africa.[27] The following patient appears to be the second documented example of Goodpasture's syndrome in South Africa.

CASE REPORT

The patient, a Coloured male carpenter, aged 21 years, was admitted to Groote Schuur Hospital on 16 November 1964.

History

For 4 months before admission the patient had repeated episodes resembling influenza, characterized by myalgia, headaches and coughing, but he continued to work. During this time he had recurrent small attacks of haemoptyses (about 12 all told), spitting up about a teaspoonful of bright red blood, but experiencing no other associated symptoms. About 3 weeks before admission he became progressively incapacitated due to tiredness and dyspnoea on effort, even at rest; blurred vision; restlessness; giddiness; anorexia and throbbing in the head.

He continued to work, but experienced repeated fainting episodes. About this time his mother noticed some degree of puffiness of the eyelids and extreme pallor. The day before admission sudden frank haematuria occurred for which he consulted his doctor and was referred to hospital.

Interrogation failed to show any episodes of sore throat, rash, previous renal or pulmonary pathology. There was no family history of tuberculosis, no associates with a similar disease and no known exposure to noxious or chemotherapeutic agents. He had suffered no dyspepsia, melaena or haematemesis. In fact, the patient had been perfectly fit and active until the onset of haemoptysis 4 months earlier.

Physical Examination

On admission. He was an extremely pale, well-built young male, not toxic but mildly pyrexial—99° F. No bone tenderness, oedema, icterus, clubbing, purpura, bruising or significant lymphadenopathy were noted. No evidence of embolic phenomena or dehydration was obtained. The fauces were slightly reddened.

Cardiovascular system. The pulse was 120/minute and regular; the blood pressure measured 105/70 mm.Hg. The venous pressure was normal. There were no cardiac murmurs and the peripheral pulses were equal and synchronous. No bruits were detected over the peripheral vessels. He was not dyspnoeic at rest; full thoracic respiration rate was 22/min. Examination of the chest showed diffuse coarse bilateral crepitations and basal rhonchi. Abdominal examination was normal; the kidneys were neither enlarged nor tender.

Central nervous system. No abnormality except for numerous fleshy flame-shaped haemorrhages and occasional hard exudates in both fundi were found. There was no evidence of arteriolar degeneration. The optic discs were normal.

Special Investigations

X-ray examination of the chest showed a normal heart, but a diffuse pulmonary infiltration was seen, extending from both hila in a fanwise manner, most marked on the right side and at the bases (Fig. 1). Close magnification study of the parenchyma showed a fine stippled punctate lesion and the pathology appeared intra-alveolar rather than in the interstitial tissue.

Straight X-ray examination of the abdomen was normal.

Intravenous pyelography was technically unsatisfactory because of the elevated blood urea, but showed normal-sized kidneys and no calcification.

Barium meal suggested an active duodenal ulcer.

Biochemical determinations gave the following results. Serum sodium 137 mEq./l.; serum potassium 4·4 mEq./l.; serum chloride 100 mEq./l.; serum bicarbonate 21·5 mEq./l.; blood urea 80 mg./100 ml.; blood cholesterol 189 mg./100 ml.; total serum bilirubin 0·4 mg./100 ml.; serum alkaline phosphatase 3·5 units; thymol turbidity 1; zinc turbidity 3; serum electrophoretogram showed a normal pattern—albumin 3·4 G/100

ml.; serum globulin 1·0 G/100 ml.; serum iron 27·1 μg./100 ml.; total iron-binding capacity 402·1 μg./100 ml.; percentage saturation 6·8%; creatinine clearance 28·5 ml./min.; serum fibrinogen—normal; and the urinary and faecal screening tests for porphyrin were negative.

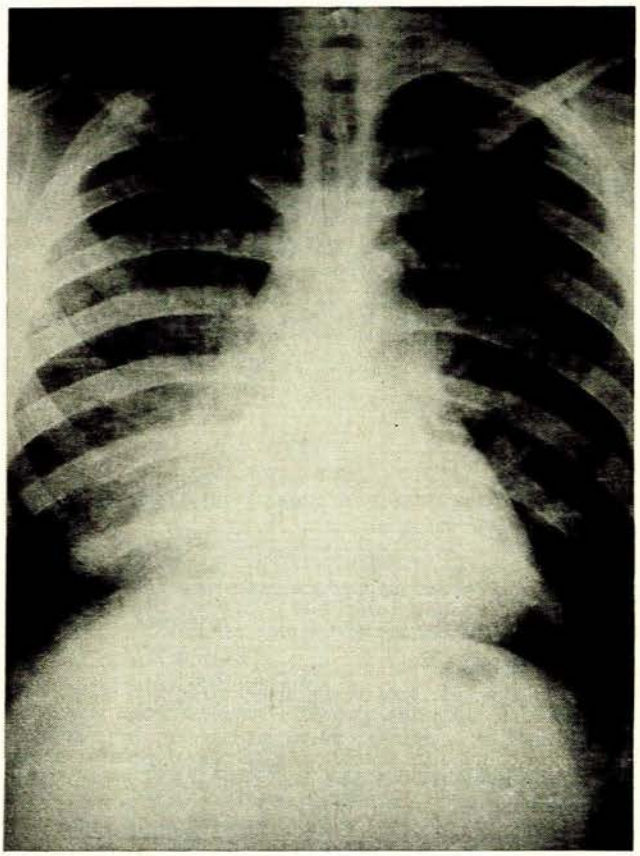

Fig. 1. Straight P-A radiograph of the chest, showing diffuse mottled opacities spreading from the hila (right more marked than left). Lesions spread to periphery and are more severe in lower lobes. No cardiomegaly.

Sputum cytology showed numerous iron-laden macrophages and some epithelial squames. Culture of fresh sputum showed no pathogens. Gram and Ziehl-Neelsen stains failed to show pus cells or pathogens. Repeated 24-hour sputa showed no acid-fast bacilli.

Urinalysis. Repeated 24-hour urinary protein estimations ranged between 4·0 and 6·0 G/24 hours. Gram stain and culture of mid-stream urine specimen showed no growth or organisms; however, the specimen contained numerous red blood cells (50/high-power field) and leucocytes (40/high-power field), but no casts. Macroscopically the specimen was smoky, had an SG of 1·016 and was otherwise biochemically normal. Repeated 24-hour urine specimens showed no pathogens; acid-fast bacilli *not* resembling *Myobacterium tuberculosis* (? *Myobacterium smegmatis*) were seen on 1 occasion. Kirschner culture and guinea-pig inoculation of urine were negative for tuberculosis.

Blood examination showed the following results: Haemoglobin 2·0 G/100 ml.; packed cell volume 12%; mean corpuscular haemoglobin concentration 32%; reticulocyte count 1·5%; peripheral smear normal, apart from an occasional poikilocyte; white cell count 15,000/cu.mm.; differential count —83% polymorph neutrophils, 16% lymphocytes, 1% polymorph eosinophils; platelet count 336,000/cu.mm.; Cuff test negative; bleeding time 2 minutes; repeated search for LE cells negative; prothombin time 88%. Sternal bone marrow showed a cellular marrow with an active white cell series especially at the later neutrophil stage; red cell series active with considerable iron deficiency; platelets plentiful. Antistreptolysin titre: less than 50 Todd units. Direct and indirect Coombs test negative; cold agglutinins and cryoglobulins were not detected. Red cell survival time (^{51}Cr) showed a half time of 16 days (but 7% of administered ^{51}Cr was excreted in the urine due to haematuria). Wassermann reaction, Mantoux reaction and Latex fixation test were negative.

Renal biopsy (using the Vim Silberman needle): 'large hypercellular glomeruli; many of the capillary loops are occluded by eosinophilic fibrin-like plugs. This material is also present in the Bowman's space, where there is capsular proliferation forming epithelial crescents. Many tubules contain red blood cells and granular red cell casts as well as colloid casts. There is some oedema and fibrosis of the interstitial tissue. The vessels show no abnormality.'

Pulmonary function studies: Arterial blood gases: pH 7·410, oxygen saturation 93%; pCO_2 28·5 mm.Hg. Lung volumes and mechanics were all normal and showed slight hyperventilation. These tests were performed shortly after admission (22 November 1964). Electrocardiogram showed sinus rhythm; PR interval 0·12 secs., normal axis; tracing within normal limits.

Course and Management

The patient was given a total of 14 pints of blood, yet the haemoglobin never exceeded 11·0 G/100 ml. There were recurrent episodes of spontaneous, painless, small haemoptyses. Frank haematuria and severe proteinuria continued throughout his stay in hospital, but the urinary deposit later showed granular casts without red cell casts. Despite restricted dietary protein intake the blood urea rose relentlessly and within weeks was about 300 mg./100 ml.: terminally the urea was 420 mg./100 ml. and the serum potassium in excess of 7·5 mEq./l. The patient was nauseous and vomited on numerous occasions.

Daily blood pressure readings showed a gradual increase in both systolic and diastolic pressure to a terminal figure of 160/110 mm.Hg. The retinal changes observed on admission cleared once the severe anaemia had been corrected by transfusion.

Therapy included anti-emetics, e.g. promethazine, trifluoperazine and chlorpromazine, the immunosuppressant agent Imuran (azathioprine),[24-26] and blood transfusions when indicated. Adrenocortical steroids were avoided because of the associated duodenal ulceration, and antibiotics were not administered.

The patient succumbed 5½ months after his initial symptoms appeared.

Postmortem Findings

Apart from a few small purpuric lesions and moderate oedema there were no other generalized abnormal features.

The lungs (combined weight, 2,914 G) presented striking aggregated pleural surface haemorrhages (0·2 cm. in size). Cut surfaces of the lungs were a dark purplish-red colour, friable and obviously intensely haemorrhagic and moist. The haemorrhagic areas occupied more than two-thirds of the lobes of both lungs; the peripheral portion of the lung was moderately well aerated. The bronchopulmonary and paratracheal lymph nodes were enlarged, soft and grey in colour. Histology of the lungs showed moderate congestion with oedema of the alveolar spaces and numerous red blood cells and siderophages in the alveolar sacs. The septal cells were swollen, prominent and some showed varying degrees of collagenization and areas of fusiform thickening. The vessels were normal. An occasional air sac was lined with a hyaline membrane-like material. The lymph nodes showed no specific changes.

The kidneys (combined weight 382 G) were pale and their outer surfaces showed small petechial haemorrhages. The cut surfaces showed swelling of the pale cortex and glomerular prominence. Cortico-medullary demarcation was distinct. The pelves and ureters were normal, as was the bladder. Histological examination of the kidneys showed a picture similar to that found at renal biopsy a month earlier, except that the glomeruli were more diffusely inflicted with evidence of sclerosis, and the tubules contained hyaline casts, red blood cells and showed hyaline droplet degeneration. The blood-vessels were

normal and the interstitial tissue was slightly oedematous (Fig. 3).

The remainder of the autopsy was non-contributory apart from cardiomegaly—left ventricular in character. The bone marrow distribution and character was normal. The duodenum appeared macroscopically normal.

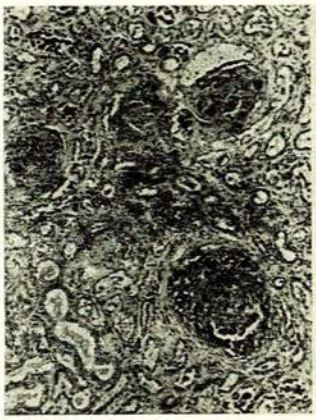

Fig. 2

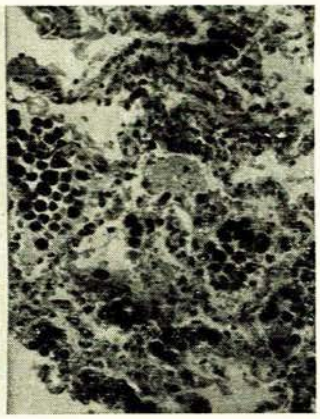

Fig. 3

Fig. 2. Microscopic appearance of kidney. The diffuse glomerulitis is evident. Note also the cast and red blood cells in the tubules—some of which are hypertrophied and dilated. (Stained H & E)

Fig. 3. Microscopic appearance of lung. There is prominence of the septal cells and striking numbers of iron-laden macrophages in the alveoli; also evident are numerous red cells and patches of oedema.

Postmortem viral studies from relevant organs have not shown any pathogens.

DISCUSSION

The case described here shows many of the characteristics of Goodpasture's syndrome reviewed by Benoit *et al.*[21] Initially there are recurrent 'flu-like illnesses followed by spontaneous small painless bright red haemoptyses for a period of 8 weeks; during this time an anaemia out of proportion to the intensity of the haemoptyses ensues. The renal facet now first manifests as frank haematuria and later rapidly passes through the stages of stormy glomerulonephritis, terminating in azotaemia. The entire disease process runs its course within 6 months. The history, symptoms, signs and investigations follow a constant pattern with few variations.

Sex, Age and Race

Benoit showed that 90% of the cases occurred in males —the majority of whom were between 16 and 30 years (yet no age group is apparently immune). Only 1 case has been reported in a Negro; all the others occurred in Caucasians.

Aetiology

No aetiologic agent has been demonstrated and present observations implicate a viral aetiology with a secondary autoimmune mechanism. Evidence has been marshalled favouring a viral aetiology—cases frequently have a history of preceding or recurrent viral-like symptoms. The initial pulmonary infection possibly results in a combination or alteration of lung tissue to produce an autoantigen and thus autoantibody production to lung tissue ensues. These lung antibodies have been shown[25,26] to cross-react specifically with glomerular capillaries in experiments on rats. This would account for the secondary rapid diffuse glomerulonephritis in Goodpasture's syndrome. Only 1 attempt to demonstrate autoantibodies in Goodpasture's syndrome has been made—this was unsuccessful.[13]

Other theories advocate an allergic basis, or arteritis and even a purpuric phenomenon.[5] The predilection of the disease for young men has led to the suggestion that androgens may play some part.

Therapy

Therapy is non-specific and uniformly ineffective. Antibiotics are without benefit. Adrenocortical steroids appear to prevent pulmonary haemorrhages[20] but have no effect on the kidneys and the mean survival time is unaffected. One case was kept alive for 60 days by repeated dialysis; however, this is only supportive and not specific therapy. Full evaluation of antimetabolic[24] or immunosuppressive agents is awaited, as the question has been broached as to whether the disease is in the 'autoimmune group'. Our attempt to evaluate the effect of immunosuppressive agents, e.g. Imuran, was thwarted by the rapid progress of the disease. Nevertheless this promises to be the future chemotherapeutic trend in this disease entity.

Some authors speculate that alteration of the androgen/oestrogen balance might be of therapeutic value. Supportive therapy in the form of blood transfusions, oral iron, anti-emetics, low protein intake and fluid balance are advocated in addition to immunosuppressive agents.

Prognosis

All but 2 cases out of a total of 53 succumbed within a period of 16 weeks from onset—half the deaths were due to azotaemia and half due to terminal severe pulmonary haemorrhage; of the 2 surviving cases (after 3 years), one is not on any specific treatment and the other is on steroids.

SUMMARY

A case of Goodpasture's syndrome—initial haemoptysis, roentgenographic evidence of pulmonary infiltration, anaemia, glomerular damage with renal failure (generally in that sequence) in a 21-year-old male is recorded. The disease ran its characteristic course and death ensued within 6 months of onset of symptomatology. Autopsy showed the pathology confined mainly to the lungs and kidneys. Viral isolation from the organs was unsuccessful. Therapy (with Imuran) during life failed to alter the natural relentless course of the disease process.

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