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Two cases of aplastic anaemia associated with tumours of the thymus

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SYNOPSIS Two cases are presented in which aplastic anaemia was associated with thymus tumours. In Case 1 the patient had a pancytopenic aplastic anaemia and was treated with A.C.T.H. The marrow showed regeneration at necropsy. The thymoma in this case was unusual as there was thymic regression with fat replacement which may have been related to A.C.T.H. Case 2 was initially of a pure red cell anaemia with but little tendency to produce a leucocytosis in response to infection and was found at necropsy to have a lymphoepithelioma of the thymus. Previously reported cases are reviewed and the role of A.C.T.H. in treatment is discussed.

The simultaneous occurrence of aplastic anaemia and a thymus tumour is uncommon, and, although 35 cases have now been recorded, the interest associated with the concurrence of these two diseases has encouraged us to present two further cases.

CASE 1 J. O'N., an interior decorator aged 41, was admitted on 21 April 1960 with a four-month history of dyspnoea, bruising, epistaxis, and a rash. The patient had no significant previous illness nor had he been exposed to benzene or its derivatives.

Examination showed pallor and generalized purpura, the liver was palpable, and Hess's test was positive. The blood count was Hb 34% (5·0 g.%), P.C.V. 18·5%, reticulocytes less than 1%, and W.B.C. 1,600 per c.mm. (672 neutrophils, 32 eosinophils, 864 lymphocytes, and 32 monocytes). A platelet count showed 19,000 per c.mm. The direct Coombs test was negative. Sternal marrow fragments were hypocellular and free cells were scanty, showing depression of all series. A diagnosis of aplastic anaemia was made and confirmed by iliac crest biopsy.

The patient was treated with fresh blood and platelet concentrated transfusions and 160 i.u. of the zinc suspension A.C.T.H. intramuscularly every third day, from 19 May 1960 until death, as part of a trial of this preparation which will be reported separately by the present authors. Deterioration was progressive and there was no real evidence that the aplasia was responding. The reticulocyte count was always less than 1% and the platelet count could only be maintained above 10,000 per c.mm. by transfusion. On 15 July the patient developed pneumonia, a pyrexia of 102°F., peripheral circulatory failure, and fresh purpura and died on 17 July. Urinary 17-hydroxycorticosteroid levels which were 48·4, 40·4, and 17·4 mg./day after the first injection of A.C.T.H. fell to 12·4, 10·6, and 5·2 mg./day on the three days before death, despite increased dosage of A.C.T.H.

At necropsy, there were petechiae and ecchymoses all over the skin and throughout the intestine. A non-encapsulated, lobulated, fatty tumour of the thymus, weighing 63 g., was attached to, but had not invaded, the pericardium, great vessels, and trachea. The cut surface was a uniform pale pink and was slightly greasy, showing no areas of haemorrhage or necrosis. The sternal and vertebral bone marrow was pale and fatty. Both adrenal glands were enlarged and there was some haemorrhage into their substance.

Sections of the thymus gland (Fig. 1) showed the tissue to be predominantly fatty, with bundles of oedematous connective tissue, in which were scattered lymphocytes and large cells with clear or reticular nuclei, and areas of persistent thymic tissue consisting mainly of small lymphocytes, in some of which Hassall's corpuscles could be seen. The bone marrow was very fatty, but areas of intense cellular proliferation were present, the predominant cells being haemocytoblasts (Fig. 2). Comparison with the original marrow (Fig. 3) showed a dramatic alteration in haemopoiesis. The spleen and lymph nodes showed lymphoid regression due to A.C.T.H. The adrenals were congested, the sinusoids dilated and engorged with areas of haemorrhage. There was hydropic degeneration of the cells of both cortex and medulla.

CASE 2 Mrs. L. H., aged 42, was admitted in April 1951 with confluent bronchopneumonia and a pyrexia of 101·4°F. She had previously had nine attacks of pneumonia, treated with penicillin and sulphonamides. She had had no contact with benzene or its derivatives. The total W.B.C. count was 7,000 per c.mm. (2,660 neutrophils, 140 eosinophils, 4,060 lymphocytes, and 140 monocytes). A chest radiograph showed interstitial fibrosis and at screening a lobulated mass was seen in the

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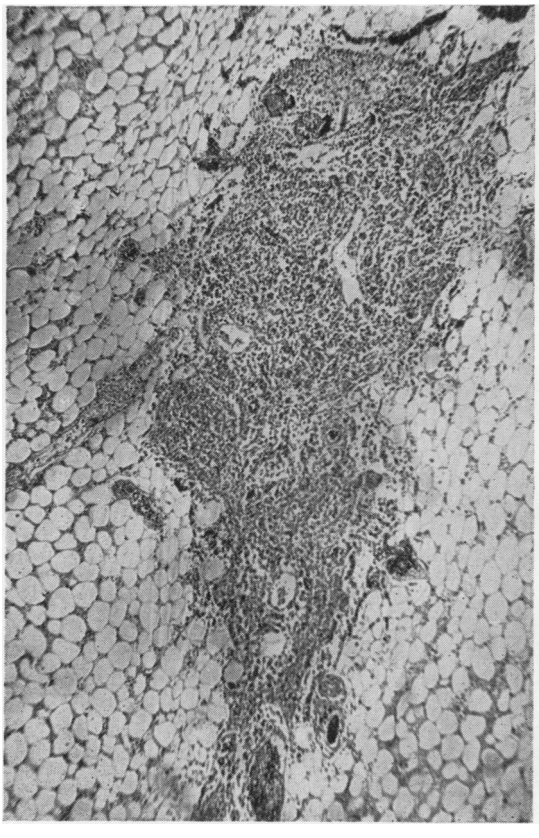

FIG. 1

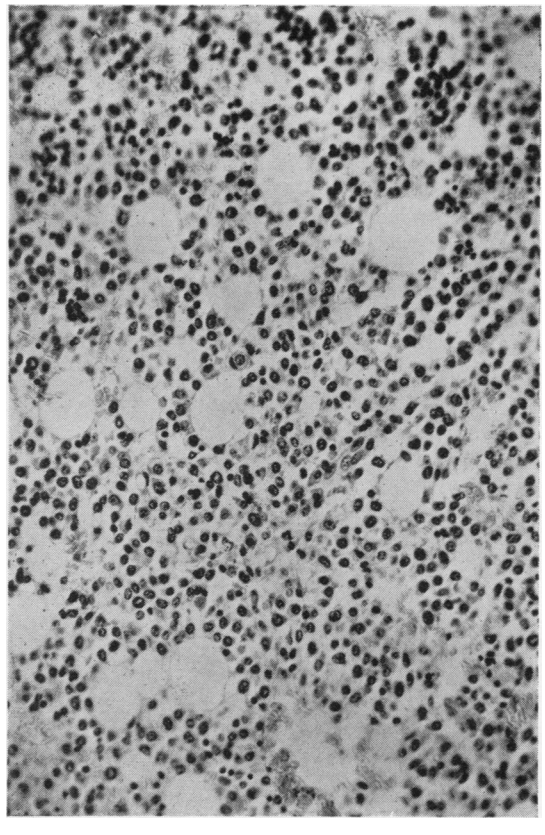

FIG. 2

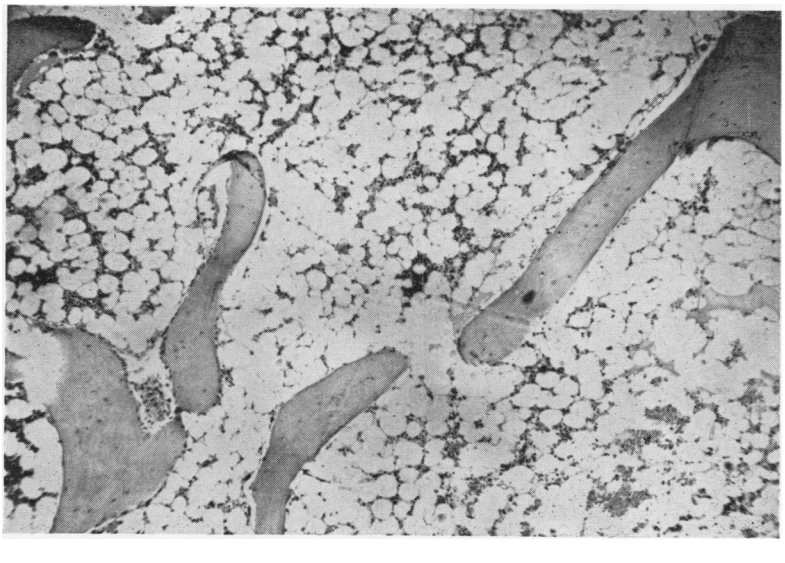

FIG. 3

FIG. 1. *Case 1. Section of thymus tumour, showing areas of persistent thymic tissue despite widespread fatty infiltration* (× *50*).

FIG. 2. *Case 1. Section of bone marrow at necropsy, showing areas of active haemocytoblastic proliferation* (× *250*).

FIG. 3. *Case 1. Section of bone marrow before treatment, showing severe hypoplasia* (× *50*).

anterior mediastinum. She was treated with penicillin, sulphonamide, and also chloramphenicol to a total dosage of 24·5 g. The pneumonia resolved but after discharge she had several attacks of bronchitis and was readmitted in June 1951 with a further chest infection which responded to tetracycline. Haemoglobin was then 54% (8·0 g.%) and in the absence of haemorrhage fell in a week to 44% (6·5 g.%) with a R.B.C. count of 2,090,000 per c.mm. and a W.B.C. count of 6,500 per c.mm. (2,860 neutrophils, 260 eosinophils, 130 basophils, 130 monocytes, 3,120 lymphocytes). *H. influenzae* was isolated from the sputum and after evaluation of the sensitivity to streptomycin this drug was given, with marked improvement in the patient's general and pulmonary condition, for a period of 14 days. One month after admission her blood count was: Hb 41% (6·1 g.%), R.B.C. 2,050,000 per c.mm., P.C.V. 18·5%, M.C.V. 77·5 $c\mu$., M.C.H. 30·5 $\gamma\gamma$, M.C.H.C. 33%, M.C.D. 6·7 μ, and W.B.C. 8,500 per c.mm. (1,615 neutrophils, 680 eosinophils, 5,695 lymphocytes, and 510 monocytes). The total serum proteins were 5·95 g. per 100 ml. (5·0 g. albumin and 0·95 g. globulin). One week later, the haemoglobin was 28% (4·1 g.%) and the reticulocyte count only 0·6%. Sternal marrow then showed 'no undisputed red cell precursors, but the cells of the myeloid series are present in normal proportions'. The haemoglobin continued to fall despite transfusions; neither vitamin B_{12}, folic acid, A.C.T.H. (25 mg. eight hourly for 15 days) nor cortisone (100 mg. daily for 19 days) had any effect on the anaemia.

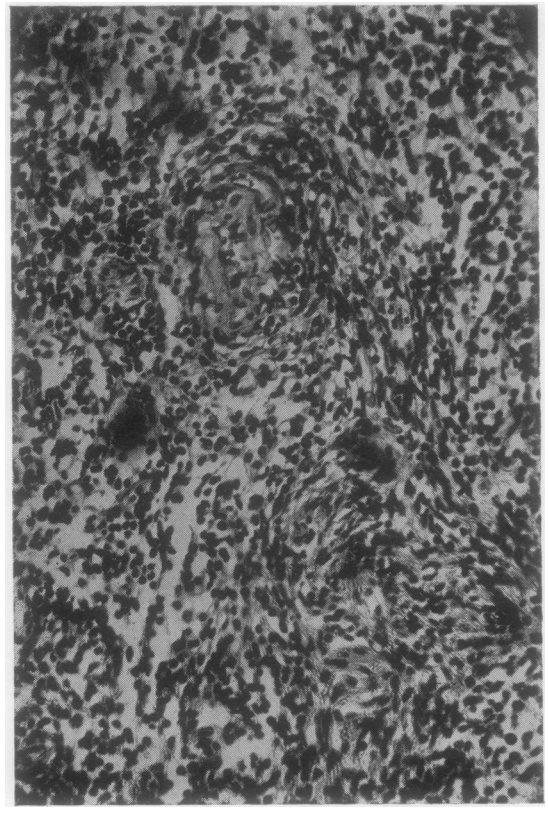

FIG. 4. *Case 2. Section of the lymphoepithelioma of the thymus, showing lobules of pleomorphic cells* (× *250*).

A further attack of bronchopneumonia in September 1951 responded to penicillin and streptomycin although the W.B.C. remained at 7,500 per c.mm. with only 5,229 neutrophils.

For the next year Mrs. L. H. was maintained with monthly blood transfusions and occasional courses of penicillin, but in November 1952 she noted spontaneous bruising. Her platelet count was then 140,000 per c.mm. and W.B.C. only 1,400 per c.mm. In December 1952 she died in a further attack of bronchopneumonia, her W.B.C. count being only 1,700 per c.mm.

At necropsy (Dr. M. O. Skelton) there was a tumour 9 × 4 cm. in the upper anterior mediastinum, which was hard and fibrous and on section had the appearance of thyroid tissue. There was emphysema and bronchitis and many small firm nodules were palpable in both lungs. The histology of the mediastinal mass revealed lobules of pleomorphic cells with small hyperchromatic nuclei, among which Hassall's corpuscles could be seen (Fig. 4). The lobules were separated by bands of fibrous tissue and there was a diffuse lymphocytic infiltration. The marrow showed a moderate number of white cell precursors and lymphocytes, but very few primitive erythroid cells. The lung showed emphysema with congestion, the nodules being areas of old organizing pneumonic consolidation, with superimposed acute inflammation.

DISCUSSION

The two cases now presented are similar to most of the 32 cases reviewed or recorded by Havard and Bodley Scott (1960). Our two cases and the three other cases presented by Wintrobe (1951), Couespel, Gaillard, and Vaillant (1960), and Freeman (1960) respectively bring the total number of occasions where this syndrome has been recognized and recorded to thirty-seven.

Twenty of the previously recorded 35 cases, as did our Case 2, showed a pure red cell aplasia. The remainder had leucopenia, thrombocytopenia, and/or complete aplasia, as in our Case 1. In addition, the second patient had a hypoglobulinaemia similar to the cases described by Ross, Finch, Street, and Strieder (1954), by Ramos (1956), and by Lambie, Burrows, and Sommers (1957), an association first reported by Good (1954); its significance is uncertain. The tumour in Case 2 was a relatively poorly differentiated lymphoepithelioma (Willis, 1953) of low malignancy and was histologically similar to many of those reported. However, the histology of the tumour in Case 1 is most unusual. The appearance is not unlike that of the regressing thymus at puberty, but the age of the patient and the

weight of the tumour make this unlikely. On the other hand, it is very similar to those lipomata of the thymus recorded by Shillitoe and Goodyear (1960) and by Dunn and Frkovich (1956). None of the 18 cases reviewed by the former authors had associated aplastic anaemia and were larger asymptomatic tumours. If, in fact, the tumour is a lipoma, then this is the first recorded case of aplastic anaemia associated with a thymic lipoma. The aetiology of this syndrome is uncertain. The occurrence of the tumour several years before the anaemia in the cases described by Humphreys and Southworth (1945), Chalmers and Boheimer (1954), Ross *et al.* (1954), Ramos (1956), Bayrd and Bernatz (1957), Lambie *et al.* (1957), Clarkson and Prockop (1958), Jacobs, Hutter, Pool, and Ley (1959), and Kurrein (1959) makes improbable the suggestion (Ross *et al.*, 1954) that anaemia is a factor in the development of the tumour. Chalmers and Boheimer (1954) suggested a common endocrinological aetiology because the eventual remission of the anaemia in their two cases followed A.C.T.H. Our findings in Case 1 support this theory. The normal adult thymus atrophies as a response to steroid therapy (Selye, 1949), and this fact associated with the findings in this patient of lymphoid regression in the thymus, spleen, and lymph nodes, plus the obvious marrow regeneration, led us to consider the possibility of regression of a true thymoma associated with remission of the aplastic anaemia, resulting from A.C.T.H. therapy. Chalmers and Boheimer's two patients received A.C.T.H., but also underwent splenectomy and thymectomy. The possibility that A.C.T.H. may be an effective therapy for the thymoma as well as for the aplastic anaemia is only a working hypothesis which we propose to test at the earliest opportunity.

These considerations suggest that the thymoma may be responsible for the anaemia, and this is supported by Havard and Bodley Scott's (1960) statement in their review that no patient has been recorded as deriving benefit from steroids or haematinic drugs before removal or irradiation of the thymus, although since then Couespel *et al.* have recorded a case that showed some improvement in the blood count before thymectomy while being treated with steroids alone. The results of such treatment, however, are inconsistent. Of 16 patients submitted to thymectomy (Humphreys and Southworth, 1945; Barquet Chediak, Fuste, and Vazquez Rosales, 1953; Chalmers and Boheimer, 1954; Ross *et al.*, 1954; Bakker, 1954; Bayrd and Bernatz, 1957; Lambie *et al.*, 1957; Clarkson and Prockop, 1958; Jacobs *et al.*, 1959; Parry, Kilpatrick, and Hardisty, 1959; Couespel *et al.*, 1960; Freeman, 1960), two died post-operatively and only nine patients showed any improvement. In the cases described by Humphreys and Southworth (1945), Chediak *et al.*, (1953), Bakker, (1954), and Jacobs *et al.* (1959) the response was immediate, while in one case the improvement was delayed (Ross *et al.*, 1954). In the case recorded by Parry *et al.* (1959), steroids were also required, and in the two cases of Chalmers and Boheimer (1954) splenectomy was also performed. Four patients (Rakojević and Hahn, 1935; Green, 1958; Jacobs *et al.*, 1959; Havard and Bodley Scott, 1960) have been treated with irradiation of the mediastinum, without improvement; two of these later received steroids and one of them (Havard and Bodley Scott, 1960) had a complete remission.

Adrenocorticotrophic hormone may have been a factor in the ultimate collapse of Case 1. The presence of a systemic infection, a platelet count less than 10,000 per c.mm., and low steroid excretion in the last three days of life may be related to the haemorrhagic and degenerative state of the adrenals at necropsy, although the changes do not amount to a frank adrenal apoplexy. These changes may represent a type of acute adrenal insufficiency similar to the Friderichsen-Waterhouse syndrome, and in retrospect, it might have been better to have treated this terminal phase with hydrocortisone as replacement therapy rather than to have increased the stimulation of the failing adrenals with more A.C.T.H.

In Case 1 the treatment of the anaemia was of little benefit, the patient having received various haematinics and short courses of cortisone and A.C.T.H. without avail, although it is possible that had hormone therapy been continued it might have been beneficial. We do not believe that the initial course of chloramphenicol given to this patient is related to the aplastic anaemia. Scott, Cartwright, and Wintrobe (1959) discussed this relationship and concluded that severe marrow depression is most likely following prolonged use of the drug. Hodgkinson (1954) noted that aplastic anaemia usually followed large doses and the majority of his patients had taken two to four times the normal maximum dose of 2 to 3 g./day. Our patient received 24·5 g. over seven days, and although chloramphenicol cannot be excluded as an aetiological factor with absolute certainty, the presenting pure red cell anaemia associated with the thymoma and the incidental finding of hypoglobulinaemia make it most unlikely.

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