

POLYCYTHAEMIA IN RENAL NEW GROWTHS

SIR ERIC RICHES, M.C., M.S., F.R.C.S., *The Middlesex Hospital, London*

The occurrence of polycythaemia in some patients with carcinoma of the kidney is well recognized; its recorded incidence varies from 1.3% to 4.4%. It has also been found in other renal conditions, such as hydronephrosis, simple cyst, polycystic disease and benign new growth, and in a few lesions of other viscera. The condition differs from polycythaemia rubra vera (Osler's disease) in that there is no splenomegaly or raised leucocyte or platelet count.

To classify a patient as polycythaemic we have accepted the criteria of Damon *et al.*,¹ namely a haemoglobin level of at least 18 G./100 ml. (122%), a red-cell count of more than 6.3 million/c.mm., and a haematocrit of more than 55%. There is a second group of patients with raised haemoglobin levels and red-cell counts which do not, however, quite reach the required criteria; this group of patients has been recognized before by Berger and Sinkoff,² although they accepted a haemoglobin level of 17 G./100 ml. as evidence of polycythaemia.

During the past year Dr. Hillas Smith has been going through the records of the patients with carcinoma of the kidney at Middlesex Hospital, and has found 131 in whom adequate haemoglobin values and histological proof of renal carcinoma justify their inclusion in the research. He has also carried out assays of the erythropoietic activity of the plasma and of portions of tumour, normal kidney and metastases in relevant cases. The method used was the bone-marrow technique which he has described elsewhere.³ This is a biological procedure involving the determination of the mitotic index in Wistar rats after injection of the stimulating material; I do not propose to go into it in detail. My part in the research has been in the correlation of the clinical and haematological aspects of the patients in whom high haemoglobin values were found.

Material

There were 3 patients with polycythaemia as defined (group I), an incidence of 2.3%. There were 11 others,

or 8.4% of the total, with haemoglobin values of at least 15.2 G./100 ml. (105%), whom I shall describe as group II.

GROUP I—POLYCYTHAEMIC CASES (HAEMOGLOBIN 18 G./100 ML.)

Case 1 (J.P.28228)

A man of 43 whose right kidney I removed in 1943. It contained a large adenocarcinoma of high-grade malignancy, but there was no invasion of the renal vein. He was a war-time patient, and I regret that we have no record of his pre-operative haemoglobin level. In 1957, 14 years later, he returned with intermittent claudication. His haemoglobin level was 22.4 G./100 ml. (152%), and a chest X-ray showed metastases in both lungs. He was treated by right lumbar sympathectomy, anticoagulants and venesection to a total of 8 pints. This reduced the haemoglobin level to 15.4 G./100 ml. It rose again gradually, and in June 1961 he had signs of cerebral metastases; the haemoglobin level was now 17.2 G./100 ml. and 3 weeks later 18.9 G./100 ml. He died on 20 December 1961 with a haemoglobin level of 18.2 G./100 ml., 18 years after operation and at least 5 years after the appearance of lung metastases.

Autopsy showed metastases in both cerebral hemispheres and both lungs.

In July 1961 the erythropoietic activity of the plasma was found to be nearly 5 times the normal, and again in November 1961 about twice normal. Assay of postmortem material showed increased activity in the cerebral and pulmonary metastases and in the spleen, but not in the remaining normal kidney.

Comment

Survival for 18 years after removal of a kidney of high-grade malignancy is unusual, as is survival for 5 years after the appearance of pulmonary metastases.

This case is being reported in full elsewhere by Smith and Blanchard.⁴

Case 2 (S.W. K:44003)

A man of 48 with recent haematuria and pain in the left loin, had a non-functioning left kidney and a pyelogram suggestive of hydronephrosis. The blood pressure was 200/110 mm.Hg, the haemoglobin level 18.5 G./100 ml. (127%), and the red-cell count 7.75 million/c.mm.; the count was repeated with similar values. Nephrectomy was performed in November 1958 and the kidney contained a carcinoma of grade II malignancy in its upper pole with a hydronephrosis associated with a thrombosed lower polar artery obstructing the pelvi-

ureteric junction; there was no invasion of the vein. The patient was given a postoperative course of X-ray therapy.

Nine days after operation the haemoglobin level had fallen to 11.6 G./100 ml. (80%). His blood pressure after three weeks was 165/95 mm.Hg. After 9 months the haemoglobin level was 14.5 G./100 ml. (100%), but it rose to 15.1 G. (104%) after 13 months, shortly before he developed a pleural effusion and was found to have a metastasis in the left upper lobe of the lung. A year later the haemoglobin level was 14.9 G./100 ml. (102%), and 2 months later he had a spontaneous fracture of the ninth left rib. The next haemoglobin value was 15.1 G. (104%) and the latest, in January 1962, was 14.7 G. (101%). In December 1961, assay of a sample of venous blood showed a moderate increase in plasma erythropoietic activity.

The patient remains clinically well and is working as a chauffeur 4 years after operation.

Comment

The haemoglobin fell to a low level after nephrectomy, but rose again to the high normal range as metastases appeared. In spite of them he is well and working.

Case 3 (A.B. 5151)

A man of 65 had a haemoptysis in April 1953; chest X-ray and tomography showed a neoplasm in the seventh left rib. He had no urinary symptoms, but excretion urography and aortography indicated a tumour of the right kidney. Blood pressure was 220/110 mm.Hg, and the haemoglobin level was 18 G./100 ml. (122%). Right nephrectomy on 13 May disclosed a tumour in the kidney which, on section, proved to be a clear-cell adenocarcinoma of low-grade malignancy with no invasion of the vein.

Fifteen days later the haemoglobin level was 13.9 G./100 ml. (94%). Five weeks after the nephrectomy I excised the affected part of the chest wall; sections showed a growth of exactly the same histology as the renal tumour. After 3 days the haemoglobin level was 11.8 G./100 ml. (81%).

The patient remained well, but with increasing hypertension until his death from cerebral haemorrhage on 26 December 1960, 7½ years after nephrectomy.

Comment

Although this was a tumour of low grade, the presence of a blood-borne metastasis made the outlook poor and so long a survival unexpected. The haemoglobin level fell progressively as the tumour and its metastases were removed, and in the absence of further metastases there was no return of polycythaemia.

In this small number of cases of polycythaemia there was a fall in the haemoglobin level after removal of the primary growth, with a subsequent rise if metastases appeared. The patients all survived for longer periods than would have been expected from the nature of their tumours. A persistent reduction in the haemoglobin level after nephrectomy has also been noted by Barnard⁵ in 14 out of 16 cases collected from the literature.

GROUP II — HAEMOGLOBIN MORE THAN 15.2 G. BUT LESS THAN 18 G./100 ML.

The 11 cases in this group were of varying degrees of malignancy and the vein was invaded in 4 of them. Their behaviour was consistent in that after an initial fall in the haemoglobin level following nephrectomy there was an early rise to about the pre-operative level. One example will suffice.

Case 12 (J.G.M84858)

A man of 59, a known tabetic, had several haemoglobin estimations made over a period of 6 years; the haemoglobin level varied from 15.2 to 17.2 G./100 ml. (118%). In Novem-

ber 1961 he appeared with haematuria and signs of a renal tumour. The haemoglobin level was then 16.8 G./100 ml. (116%).

I removed his left kidney, containing an adenocarcinoma of low-grade malignancy, but with the vein invaded. On the following day the haemoglobin level had fallen to 14.8 G./100 ml. (102%), but after 10 days it was 15.9 G./100 ml. (110%) and after 3 months 16.6 G./100 ml. (114%). Erythropoietic assay was carried out by Dr. Hillas Smith on blood from the patient's renal artery, renal vein, and a peripheral vein, and on a piece of the tumour and a piece of normal kidney. None differed significantly from the normal control values.

Assay of the plasma from another patient in this group (case 8) was also normal, showing no significant increase in erythropoietic activity.

Comment

Of the 11 patients in group II, 5 have died and 6 are alive. One, the only woman in the series, died after 10 months from cerebral haemorrhage with no evidence of recurrence. Four lived for periods of 2½ - 4½ years. Of the 6 survivors, 2 are in their tenth year and 2 more are alive beyond 5 years; 1 is alive at 4 years and one at 1 year. Their survival compares favourably with that of a similar group without raised haemoglobin levels.

DISCUSSION

Hillas Smith has charted the haemoglobin values in the 89 male patients with carcinoma in the series. There are 2 peaks, 1 at 11 G. and 1 at 13.4 - 15.8 G./100 ml. The first includes the many anaemic patients who have had prolonged haematuria; the second includes the patients described in group II; beyond is the small group of true polycythaemics.

This curve is very similar to one made up from the figures of 116 males with carcinoma of the kidney described by Conley *et al.*⁶ Figures for 80 normal men aged 45 - 74 years were taken from a survey by Kilpatrick;⁷ the peak comes at 13.4 G./100 ml. The 2 sets can be combined and compared and show a shift to the right, or an increase in haemoglobin values in the carcinoma patients.

There is considerable evidence to support the existence of a hormone, erythropoietin, derived in part at least from the kidney.⁸ In some cases of carcinoma of the kidney it is increased in the plasma. If this is so it brings renal tumours into line with those of the thyroid, parathyroid, pancreas and suprarenal, in the ability of both the primary tumour and its metastases to produce a specific hormonal effect.

From the practical viewpoint it is evident that all patients with polycythaemia or even those with moderately raised haemoglobin values should have urological investigations, just as those with renal lesions should have haematological investigations. The evidence from this series suggests that the prognosis in carcinoma of the kidney is improved in patients with polycythaemia, and that even a raised haemoglobin level short of true polycythaemia is a beneficial factor.

SUMMARY

When true polycythaemia occurs in a case of renal carcinoma the blood picture becomes normal after

nephrectomy and remains so unless metastases occur. A return of polycythaemia may be the first indication of a metastasis. In a greater number of cases there is a raised haemoglobin level not reaching the level for acceptance as polycythaemia. In these the blood picture returns to its pre-operative level soon after operation and does not rise even if metastases appear.

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