technicians of the department of cardiology for their help with the electrocardiograms.

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“Giant Follicle Lymphoma of the Spleen”

A Condition Closely Related to Lymphatic Leukaemia but Apparently Curable by Splenectomy

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[WITH SPECIAL PLATE]

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In 1960, under the title “Giant Follicle Lymphoma of the Spleen” (Hickling, 1960), a description was given of four patients with the following features: (1) Massive splenomegaly without enlargement of superficial lymph nodes. (2) Lymphocytosis without any great increase in total leucocytes, and with the presence of abnormal and immature mononuclear cells in the circulating blood. (3) Large numbers of lymphocytes in bone-marrow aspiration films. (4) In the two cases in which bone-marrow biopsy was carried out there were numbers of lymphocyte foci in active marrow. (5) Excellent clinical result of splenectomy. (6) In the course of time the abnormal and immature mononuclear cells in the circulating blood disappeared and the leucocyte count returned to normal, the lymphocytosis disappearing. (7) In the three cases in which liver biopsy was carried out at the time of splenectomy there were abnormal lymphocyte accumulations in the portal tracts. (8) No superficial lymph-node enlargements occurred during the periods of observation, and the patients remained well.

The object of this paper is to examine the relation of the four cases previously described, and a fifth case seen since that paper was written, to chronic lymphatic leukaemia. Summaries were given of the first four cases in the paper already referred to, but brief summaries are given here of these four cases and a longer report of the fifth case, hitherto undescribed.

Case 1

A woman aged 34 when first seen in September 1952 complained of lack of energy for 18 months and increasing abdominal swelling for two months. Splenomegaly was present, there was no anaemia, and the leucocytes in the circulating blood varied between 10,000 and 15,000/c.mm., of which 75 to 80% were lymphocytes, with 2 to 9% of immature and abnormal forms. Sternal puncture in 1952 and 1953 showed a predominantly lymphatic bone-marrow. X-ray therapy of the spleen and, later, a course of nitrogen mustard intravenously caused a very temporary effect only on the size of the spleen and on the general health, and produced transient

leucopenia. Splenectomy in February 1954 produced an excellent clinical response. By February 1955, one year after splenectomy, the total and differential leucocyte counts in the circulating blood were normal, and no abnormal cells were seen.

The histology of the spleen was that of giant follicle lymphoma. Many enlarged lymphatic glands were found in the abdomen, but these were not removed, except those which came away with the spleen and which showed similar changes to that of the spleen. Liver biopsy showed accumulations of lymphocytes in the portal tracts. The patient remained well 10½ years after splenectomy, the circulating blood remained normal, and no enlargement of lymph nodes had occurred. No histological examination of the bone-marrow was made in this case.

Case 2

In April 1956 a woman, then aged 43, was first seen on account of thrombosis of the central artery of the retina in the left eye. For four months she had had abnormal tiredness, colicky abdominal pains, and diarrhoea with a feeling of pressure in the abdomen. Splenomegaly and a mild anaemia were present, the leucocyte counts were about 5,000/c.mm., of which over 60% were lymphocytes, with about 4% of abnormal and immature forms. Sternal-marrow-puncture films revealed large numbers of lymphocytes. Bone-marrow biopsy showed the presence of lymphocyte foci in an active bone-marrow (Special Plate, Fig. 1). Three separate courses of x-ray treatment of the spleen caused some decrease in size of the organ and some improvement in general health, but these were transitory.

Splenectomy in April 1959 produced an excellent clinical result. At operation another bone-marrow biopsy again showed numbers of lymphocyte foci in an active bone-marrow, liver biopsy showed lymphatic accumulations in the portal tracts (Special Plate, Fig. 2), and the histology of the lymph nodes in the hilum of the spleen and the histology of the spleen itself (Special Plate, Fig. 3) were more like those of giant follicle lymphoma than of lymphatic leukaemia. Large numbers of lymph nodes were present in the abdomen, but no attempt was made to remove them. The circulating blood gradually became normal, but by August 1959 a few abnormal and immature mononuclear cells were still present in the circulating blood. Five years after splenectomy the patient was well, with a

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normal circulating blood, and no enlargement of lymph nodes had occurred.

Case 3

During a routine examination in 1938 for some trivial illness the patient, a woman then aged 67, was found to have a large spleen. The splenomegaly produced no symptoms until 1942, when she had abdominal pains and distension, constipation, and loss of weight. There was very mild anaemia, total circulating leucocytes were normal, but there were between 68 and 82% of lymphocytes, with many immature and abnormal forms, and diminished number of platelets. Sternal-puncture films showed that almost all the cells were lymphocytes or lymphoblasts.

Splenectomy in October 1943 produced an excellent clinical result. She survived for 13½ years after splenectomy, and never developed any other signs of haematological disease, but died of pneumonia in February 1957, aged 86. At necropsy no sign of any lymphatic disease was found. The liver contained no lymphatic accumulations, and two lymph nodes from different parts of the body showed no sign of disease. In this case bone-marrow biopsy was not carried out, nor was liver biopsy at the time of operation. The abnormal circulating blood persisted until May 1952, nine years after splenectomy. During this time the total leucocytes were normal, but there was a lymphocytosis at almost every examination, with a few abnormal and immature forms. By October 1952 the total and differential leucocyte counts had become normal and remained so in 1953, 1954, and 1955. Histological examination of the spleen showed large, irregular follicles composed mostly of lymphoblasts, and there were many lymphocytes and lymphoblasts in the splenic pulp. The appearances were more like those of lymphatic leukaemia than of giant follicle lymphoma, but as there is a known close connexion between giant follicle lymphoma and lymphatic leukaemia, and as the whole clinical and haematological picture was just the same as in the preceding cases, this case was included in the series.

Case 4

A man aged 51 when first seen in May 1958 complained of excessive tiredness. Moderate anaemia and splenomegaly were present. White cells numbered 8,000–10,000/c.mm., of which over 80% were lymphocytes, with 2 to 11% of immature and abnormal cells. Sternal-puncture films showed an excess of lymphocytes. Bone-marrow biopsy (Special Plate, Fig. 4) revealed many lymphocyte foci in an active bone-marrow. X-ray treatment of the spleen caused slight diminution in size with increased comfort, but the effect was transient and the haemoglobin fell to 35%. He was given blood transfusions and sent home. He was readmitted in October 1958 with profound anaemia, and the total and differential leucocyte counts were as before. Splenectomy in October 1958 produced an excellent clinical result. Many enlarged lymph nodes were seen and felt in the abdomen at operation, but no attempt was made to remove them, except those that came away incidentally with the spleen.

The circulating blood had not become quite normal a year after splenectomy, but since then the total and differential leucocyte counts have gradually become normal and no abnormal cells have been found in the circulating blood. He remained well with a normal blood six years after splenectomy. Liver biopsy (Special Plate, Fig. 5) showed accumulations of lymphocytes in the branches of the portal tract. The spleen (Special Plate, Fig. 6) and lymph nodes (Special Plate, Fig. 7) showed very large ill-defined lymphatic follicles with lymphocyte accumulations in the pulp, the appearances being more like that of lymphatic leukaemia than of giant follicle lymphoma.

Case 5

A woman aged 71 when first seen in January 1963 complained of intense tiredness and loss of weight of three months' duration. For about a year she had noticed indigestion with a feeling of pulsation in the left side of the abdomen. On examination she was found to have massive splenomegaly, the margin of the spleen extending to ½ in. (1.3 cm.) beyond the midline and crossing the midline 2 in. (5 cm.) above and 2 in. (5 cm.) below the umbilicus. There was no enlargement of superficial lymph nodes or of the liver.

She had had a febrile illness in 1959, in the course of which she was found to have an enlarged spleen, not big but easily palpable.

Blood examinations showed mild anaemia, haemoglobin being about 75%. The leucocyte counts were as follows: February 1963, total leucocytes 6,000/c.mm. (neutrophils 31%, monocytes 9%, eosinophils 4%, basophils 1%, lymphocytes 50%, abnormal and immature lymphocytes 5%); May 1963, total leucocytes 7,000/c.mm. (neutrophils 37%, monocytes 8%, eosinophils 2%, basophils 1%, lymphocytes 50%, abnormal and immature lymphocytes 2%); June 1963, total leucocytes 7,500/c.mm. (neutrophils 39%, monocytes 8%, lymphocytes 49%, lymphoblasts 1%, other immature and abnormal lymphocytes 3%). Platelets were normal on each occasion.

Sternal-marrow puncture showed a great excess of lymphocytes. Bone-marrow biopsy showed the presence of large masses of lymphocytes in an otherwise normal bone-marrow, there being no general lymphatic infiltration.

As a result of experience with the previous four cases, prolonged observation was not considered necessary and splenectomy was carried out on 1 July. The clinical result was excellent, and all trace of abnormal tiredness soon disappeared. Examination of the circulating blood showed a transient neutrophil polymorphonuclear leucocytosis, but within a month the total and differential leucocyte counts reverted to the pre-operative condition of a moderate lymphocytosis. There was a considerable increase in platelets after splenectomy. The patient was in excellent health one year after splenectomy, with no enlargement of superficial lymph nodes or liver, but the circulating blood had not yet become normal. There was no anaemia, platelets were still increased, total leucocytes were normal, but lymphocytes numbered 40%, with 4% of immature and abnormal forms. Histology of the spleen showed many Malpighian bodies to be very large, with ill-defined margins, and with much lymphatic infiltration into a congested pulp. Histology of a lymph node which came away with the spleen showed very large lymph follicles and lymphatic infiltration into the pulp. The liver showed the presence of lymphocyte accumulations in the portal tracts, similar to those found in cases of lymphatic leukaemia but not so large.

Summary of Findings in the Five Cases

Four of the patients were women aged 36, 46, 71, and 72 at the time of splenectomy, and one was a man aged 51.

Spleen

The massive splenomegaly was discovered during the investigation of tiredness, weakness, and loss of weight in two patients; of tiredness, weakness, and abdominal pains in two patients; and of abdominal pains, diarrhoea, and occlusion of a branch of a central artery of the retina in one patient. The spleen was massive in all five patients, reaching to the midline of the abdomen both above and below the umbilicus, or beyond this. The massive splenomegaly when first seen suggests a slow and insidious onset of the disease. The enlarged spleen was known to have been present for five years before splenectomy in one patient, for three years in two patients, and for two years in two patients, but one female patient on reviewing her symptoms thought that it might have been present for 10 years.

The period during which the massive splenomegaly developed is known only in Case 5, in which three years before splenectomy the spleen was just palpable, and it reached beyond the midline of the abdomen at the time of splenectomy. In the other four cases the massive splenomegaly remained of about the same degree during the periods of observation mentioned.

In two patients the histology of the spleen was that of giant follicle lymphoma—the follicles were very large, had well-marked germinal centres, and were fairly well defined, with the pulp of the spleen lying packed tightly between the follicles. In the other three spleens, however, the histological picture was more like that of lymphatic leukaemia—the follicles were large, but not well defined, and there was much lymphatic infiltration

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FIG. 1

FIG. 2

FIG. 3

FIG. 1.—Case 2. Section of bone-marrow, showing two lymphocyte foci close together in a somewhat hyperplastic bone-marrow.

FIG. 2.—Case 2. Section of biopsy of liver, showing lymphocyte accumulations in portal tract.

FIG. 3.—Case 2. Section of spleen, showing giant follicles. This patient is well, with a normal circulating blood, five years after splenectomy.

FIG. 4.—Case 4. Section of bone-marrow, showing a large, fairly well localized mass of lymphocytes in a hyperplastic bone-marrow.

FIG. 5.—Case 4. Section of liver biopsy specimen, showing accumulations of lymphocytes in portal tract.

FIG. 6.—Case 4. Section of spleen, showing large follicles and lymphatic infiltration into the pulp.

FIG. 7.—Case 4. Section of lymph node from abdomen, showing large lymph follicles and lymphatic infiltration into the pulp. This patient is well, with a normal circulating blood, six years after splenectomy.

FIG. 4

FIG. 5

FIG. 6

FIG. 7

into the pulp as well and also excessive amounts of red blood cells in the pulp.

In spite of the fact that the histology of the five spleens was not the same, nevertheless it is thought that the patients belonged to one group because the rest of the features of all five cases are the same, and because of the known close association between giant follicle lymphoma and lymphatic leukaemia. The relation of giant follicle lymphoma to lymphatic leukaemia, the occurrence of splenomegaly in giant follicle lymphoma, and the changes in the bone-marrow and blood of that disease were considered in a previous paper (Hickling, 1960). The name "giant follicle lymphoma of the spleen" seems the most suitable for this group of cases. The lymph follicles in all the cases are very large, but in three of them they are not so well defined, with the appearance of compression of the pulp between the follicles, which occurs in typical cases of giant follicle lymphoma.

Circulating Blood

Only one patient had a severe anaemia at any time. In the others there was either no anaemia or very slight anaemia. In all cases the total leucocyte counts were normal or moderately raised, but all had a lymphocytosis, the percentage of lymphocytes varying between 52 and 80. All had numbers of abnormal and immature mononuclear cells in the circulating blood, including lymphoblasts. The abnormal and immature mononuclear cells were of various types, some being definite lymphoblasts, others having an appearance intermediate between that of lymphocytes and monocytes, and some being large cells with nucleoli but without having the other characteristics of lymphoblasts. Platelets were normal in four patients and diminished in one before splenectomy.

After splenectomy any anaemia present was quickly relieved, and in the four patients in whom immediate post-operative blood counts were carried out there occurred a transient neutrophil polymorphonuclear leucocytosis and a rise in platelets of much longer duration. In these the leucocytosis soon subsided and the lymphocytosis reappeared, but gradually the percentage of lymphocytes fell and that of the polymorphonuclear leucocytes rose until a completely normal leucocyte picture was present. This change to normal circulating blood took different times to occur in these cases. The blood was normal four months after splenectomy in one case, one year after in a second, two years after in a third, and the change took nine years to occur in one case; in Case 5 the blood had not become normal one year after splenectomy. Once the blood became normal it remained so for the remainder of the period of observation.

Bone-marrow

In all five patients ordinary bone-marrow-puncture films showed excessive numbers of lymphocytes and most also showed lymphoblasts in varying proportions, in some practically all the cells in the films being lymphocytes and lymphoblasts.

Bone-marrow sections made after rib biopsy in three patients showed the presence of lymphocyte foci in the bone-marrow, which was otherwise normal in two patients and hyperplastic in the third. These foci of lymphocytes had no germinal centres, they were small with deeply staining cells in two patients, but large with paler staining cells in the third patient. In some patients they were far apart, and bone-marrow-puncture methods of obtaining specimens for section might have failed to produce bone-marrow showing any lymphocyte foci (McFarland and Dameshek, 1958; Woodliff, 1963).

At Charing Cross Hospital a special trephine is used by means of which a semi-circle of bone is removed from a rib at open operation (Hickling, 1958).

Liver

Liver biopsy was carried out at the time of splenectomy in four patients, and in all of these there was an abnormal accumulation of lymphocytes in the branches of the portal tract, but not as large accumulations as those usually seen in cases of lymphatic leukaemia.

Lymph Nodes

No superficial lymph-node enlargement was present in any patient, nor has any developed since splenectomy. In three patients large numbers of enlarged lymph nodes were found in the abdomen at operation for splenectomy, but only those nodes that incidentally came away with the spleen were removed. In two patients the histology of these nodes was that of giant follicle lymphoma, which was the histological change in the spleen of these two patients, and in the others there was great enlargement of lymph follicles, but they were ill defined and there was also lymphatic infiltration into the medulla, the appearances being similar to that found in lymphatic leukaemia. There has been no evidence that any lymph-node enlargement in the abdomen has persisted or caused any trouble since splenectomy.

Treatment Before Splenectomy

Three patients had deep x-ray treatment to the spleen, and one of these also had a course of nitrogen mustard injections. In all these cases very little diminution in size of the spleen occurred, though all developed leucopenia, and the patients felt little or no benefit from the treatment.

Duration and Progress

One patient died of pneumonia 13½ years after splenectomy, and at necropsy two lymph nodes from different parts of the body were normal and liver histology was normal. The other four patients are all well, one 10½ years, one six years, one four years, and one one year after splenectomy.

Comments

There seems to be no doubt that these five cases belong to one group, although the features are incomplete in some. Bone-marrow biopsy was not carried out in two cases and liver biopsy in one case at the time of splenectomy. But in all five cases the histology of the spleen was that of a "lymphoma," the findings being those of giant follicle lymphoma in two and more like that of lymphatic leukaemia in the other three. All had large numbers of lymphocytes, and some lymphoblasts also, in bone-marrow-puncture films.

The histology of the liver in the four cases examined was that of lymphatic leukaemia, though the accumulation of lymphocytes in the portal tracts was not as large as that seen in typical cases of lymphatic leukaemia, and all five had changes in the circulating blood of the type seen in aleukaemic lymphatic leukaemia.

The excellent health and gradual reversion of the circulating blood to normal strongly suggests that a "cure" is obtained by splenectomy.

Many patients with splenomegaly of various kinds may benefit from splenectomy either because of the relief obtained from the removal of a large, heavy mass from the abdomen, or because of the relief of "hypersplenism," that is to say, an apparent inhibition by the spleen of the discharge of erythro-

cytes, leucocytes, and platelets from a normal or hyperplastic bone-marrow, but the relief produced in the cases described in this paper is far greater than could be accounted for merely by the removal of a heavy mass from the abdomen.

With regard to the question of hypersplenism, there is very little evidence to suggest this in any of these five cases. Most had slight anaemia, all had a moderate neutropenia before splenectomy, but this persisted for varying periods after splenectomy, in one case for as long as nine years. Platelets in the circulating blood were normal in four out of the five cases, and the usual rise of platelets after splenectomy occurred in all cases.

This condition, here called "giant follicle lymphoma of the spleen," is certainly rare. A sixth case with exactly similar features has been seen through the courtesy of Dr. R. J. McGill, of the Royal South Hants Hospital. Insufficient time has elapsed since splenectomy to judge the effect.

If bone-marrow biopsy was performed more often in cases of "aleukaemic lymphatic leukaemia" with large spleens, more cases might be discovered.

Summary

A description is given of five cases with massive splenomegaly, all of which presented features of a lymphoma very similar to that of lymphatic leukaemia except that the bone-marrow contained localized masses of lymphocytes instead of generalized infiltration. All were apparently cured by splenectomy.

Acknowledgments were made in the previous paper for help in the first four cases. The fifth case was under my own care at Charing Cross Hospital, and the splenectomy and liver biopsy were carried out by Mr. Norman Tanner. Dr. T. C. Studdert, of the Cumberland Infirmary, Carlisle, gave me information about a previous illness of one patient (Case 5) in which the spleen was found to be enlarged.

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Spontaneous Dissecting Aneurysms of the Cervical Internal Carotid Artery

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[WITH SPECIAL PLATE]

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Occlusion of the internal carotid artery just beyond its origin in the neck is a not uncommon finding at necropsy. Hultquist (1942) observed it in 4.4% of a series of 1,300 routine necropsies. In most cases the occlusion is caused by thrombosis superimposed on atheromatous degeneration of the artery concerned, and the condition is therefore much commoner in the older age-groups. As a rarer occurrence it is seen in individuals below the age of 40. This arbitrary division into these two age-groups can be made, as the pathogenesis of the condition seems to be quite different in the two groups.

The causes of obstruction of the internal carotid artery in this younger category have been adequately reviewed by Humphrey and Newton (1960). They found that in over half the published cases no adequate cause could be determined. Approximately half of the remainder were attributed to recent trauma, which has been discussed by Therkelsen and Hornnes (1963). Other possible causes mentioned being cerebral aneurysm and subarachnoid haemorrhage, hypertension, blood dyscrasias, chronic infection such as rheumatoid arthritis and rheumatic fever, neoplasms, cervical ribs, and the post-partum state. Recently an arteritis of the internal carotid has been suggested (Shillito, 1963). Atheromatous occlusion appears rarely in this age-group.

In the past five years 115 patients were found to have occlusion of the internal carotid artery in the neck. Ten of these patients were below the age of 40. Of these 10, three were related to recent cerebral trauma, two were associated with chronic infective processes elsewhere in the body, one followed a severe attack of epilepsy, and in one no associated

factor was observed. The purpose of this report is to put on record the remaining three cases in which a spontaneous dissecting aneurysm was responsible for sudden partial or complete occlusion of the lumen of the internal carotid artery near its origin.

Case 1

A housewife aged 40 complained of a generalized headache for 12 hours and then suddenly developed a complete aphasia and right hemiplegia. Clinical examination revealed a drowsy individual, completely aphasic, with a right homonymous hemianopsia and a right hemiplegia. She was normotensive and apart from a systolic murmur over the cardiac apex there were no other signs of systemic disease. Her level of consciousness deteriorated. Angiography demonstrated a complete obstruction of the left internal carotid artery 1.5 cm. above its origin, no contrast medium entering the cranial cavity. It was noted that the pineal gland, which was calcified, lay to the right of the midline. Her condition continued to deteriorate and she died some 40 hours after the onset of symptoms.

Necropsy revealed no significant abnormality in the bodily organs. There was no myocardial hypertrophy and the important arteries showed only slight atheroma, with a few linear lipid plaques in both common carotid arteries. The left internal carotid artery was occluded by a dissecting aneurysm of the posterior wall which began 1 cm. above its origin and extended up to the base of the skull. A small intimal tear was present 4 mm. above the lower limit of the dissection. There were only a few small lipid plaques at the origin of the left internal carotid artery, below the dissection. The angiography puncture holes were 4 cm. lower down in the left common carotid artery, well clear of the dissection.

Examination of the decalcified skull base showed that the dissection ceased abruptly at the beginning of the bony carotid canal. Above this the lumen of the left internal carotid artery and the origins of all its branches contained fluid blood, with the exception

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