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Lymphosarcoma during the course of myeloid leukaemia

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THE co-existence of malignant lymphoma and chronic myeloid leukaemia has rarely been recorded. Because of the theoretical implications of such an association, the occurrence of lymphosarcoma in a woman with busulphan-treated chronic myeloid leukaemia is here reported.

Case report

The patient, a 52-year-old housewife and shop assistant, presented in October 1964 with complaints of excessive tiredness recently, anorexia and weight loss. The latter may have occurred over a longer period of perhaps 9 months. The only abnormal clinical findings at that time were mild pyrexia (99°F), an appendicectomy scar and a palpable spleen tip, approximately 1 in. below the costal margin.

Investigations. Hb 12.9 g/100 ml, PCV 37%, WBC 49,400/mm³; 70% of the white cells were polymorphonuclear neutrophils, 10% metamyelocytes 6% myelocytes and 2% 'blast' cells. By the time she was admitted to hospital, 3 months later, the spleen was palpable 4 in. below the costal margin, Hb had fallen to 11.1 g/100 ml and total WBC had risen to 186,900/mm³ (69 neutrophils 11% metamyelocytes, 8% myelocytes and 3% promyelocytes). Platelet count was then 793,000/mm³. Radiography revealed no evidence of hilar lymphadenopathy.

Busulphan therapy was commenced in January 1965. The courses and doses of this drug, and periodic white cell and platelet counts are shown in Fig. 1. Hb levels remained about 10 g/100 ml

until the terminal phase of the illness in September 1966.

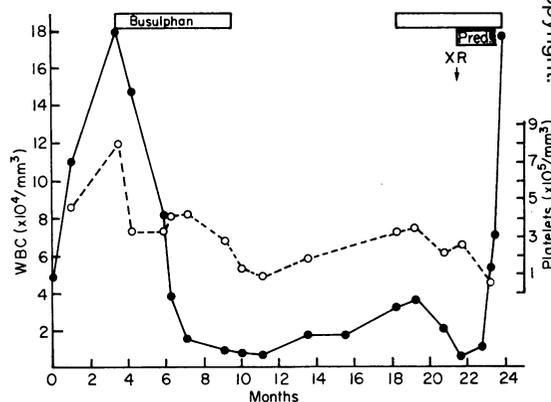


FIG. 1. Response of white cells and platelets to treatment over a 2-year period.

She began to feel well again March 1965 but was troubled by new symptoms of numbness and tingling in fingers and thumbs in July 1965. There was some blunting of pain sensation at the tips of these digits and sensory neuropathy was diagnosed. Serum B₁₂ was normal and there was no response to oral vitamin B₁. The paraesthesiae had disappeared by May 1966 and she remained well until June 1966 when she became aware of rapidly-enlarging tender lymph nodes on both sides of her neck. On examination there proved to be tender, mobile, rubbery nodes up

to 1 in. in long diameter, in the cervical, axillary and inguinal regions. Her spleen was palpable, as before, about 4 in. below the costal margin. Radiography showed bilateral hilar lymphadenopathy.

Aspiration biopsy of the right cervical lymph nodes revealed appearances of lymphosarcoma (Fig 2). Surgical cervical node biopsy revealed

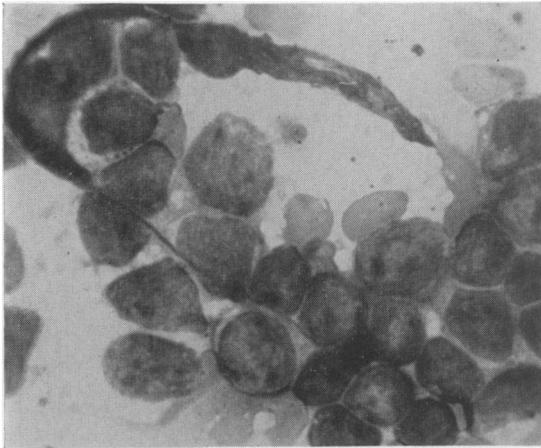


FIG. 2. Aspiration biopsy showing abnormal lymphoid cells seen in lymphosarcoma. Occasional granulated cells. (May-Grünwald-Geimsa, $\times 800$).

destruction of the normal architecture and replacement by sheets of cells in which mitotic figures were numerous. The majority of these cells were lymphocytic in type but some large, more immature, cells resembling myelocytes were also present. There was some peroxidase activity in a small proportion of the immature cells but most seemed to be of the lymphoid or reticulum cell series. Appearances were consistent with the presence of lymphosarcoma in a patient with myeloid leukaemia (Fig. 3). Sternal biopsy showed hypercellular normoblastic marrow with conspicuous increase in megakaryocytes and myeloid preponderance chiefly due to myelocytes, though with some increase in promyelocytes and myeloblasts. The peripheral blood about this time contained 9200 white cells/ mm^3 , 14% of which were primitive cells; the neutrophil alkaline phosphatase count was 5 compared with a control of 60.

The cervical lymphadenopathy responded to a course of local X-ray therapy. Oral prednisone (20 mg daily) was started during this course and the dose reduced at an outpatient attendance in August 1966, when she was very well. However, terminal acute leukaemia (WBC up to 184,000/ mm^3 with 38% blast cells) developed

towards the end of that month and did not respond to increased steroid dosage or 6-mercaptopurine. She died in hospital on 19 September 1966.

Necropsy revealed haemorrhage into the right temporal lobe of the brain and bilateral basal bronchopneumonia. There was enlargement of cervical, axillary, inguinal, hilar and intra-abdominal lymph nodes which had a fleshy appearance on section. The spleen weighed 1780 g and was the site of numerous infarcts.

Discussion

There are numerous reports in the literature of leukaemia complicating various types of reticulosis, the association between chronic lymphatic leukaemia and lymphosarcoma being particularly well recognized. Acute leukaemia may be the terminal stage of reticulum cell sarcoma (Beutler, 1954; Zeffren & Ultmann, 1960), lymphosarcoma (Sternberg, 1916; Flashman & Leopold, 1929) or Hodgkin's disease (Skworzoff, 1930; Skworzoff & Kazantzeva, 1930). The association of chronic myeloid leukaemia with malignant lymphoma, however, remains rarely recorded; the complicating disease process has been reticulosarcoma (Hanns, Israel & Sacrez, 1934; Wilcken, 1957; Belotipetskaya & Gets, 1960, lymphosarcoma (Yang, 1936; Forkner, 1938; Sardesai & Bhatia, 1959; Howell & Whitfield, 1963; Kurai & Papp, 1965; Wilson & van Slyck, 1966) and Hodgkin's disease (Samwick, Cohn & Swiller, 1955; Lacker & Sussman, 1963); Hodgkin's disease may also be

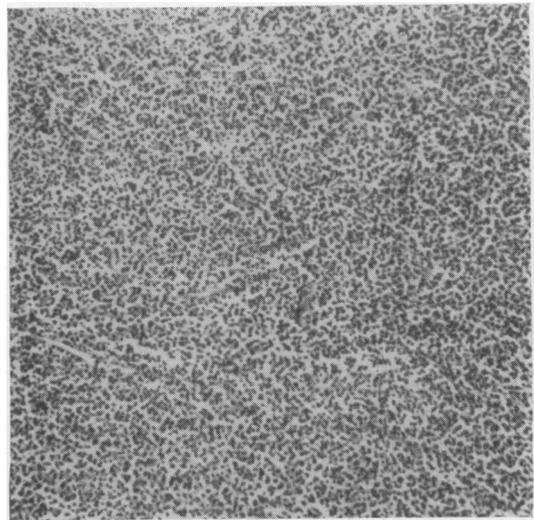


FIG. 3. Lymph-node section showing complete replacement of architecture with lymphoid cells. (Haematoxylin and eosin, $\times 80$).

TABLE 1
Co-existent myeloid leukaemia and lymphosarcoma

Reference	Age (yr)	First diagnosis	Treatment	Second diagnosis	Method	Interval between diagnosis	Clinical features	Duration from second diagnosis to death
Hanns <i>et al.</i> (1934)	34	CML	Splenic irradiation	Reticulo-sarcoma	Biopsy	Simultaneous	Soft tissue swellings	Total course 3-4 weeks
Yang (1936)	36	CML	Radiotherapy	Lympho-sarcoma	Biopsy	? 1 year (possibly simultaneous)	Generalized lymphadenopathy	? 1 year (4 months) from biopsy
Forkner (1938)		CML		Lympho-sarcoma	No other details recorded			
Introzzi (1955)	26	CML	Busulphan 6-mercapto-purine	Reticulum cell sarcoma	Autopsy	18 months	Soft tissue swellings	2 months
Konecni <i>et al.</i> (1957)	53	CML	'Sulfabutin'	Reticulum cell sarcoma	1. Aspiration 2. Autopsy	3 years	Joint pain	4 weeks
Wilken (1957) (case 1)	25	CML	Radiotherapy	Reticulo-sarcoma	Biopsy	3 years	Generalized lymphadenopathy	'Few weeks'
Sardesai & Bhatia (1959)	48	CML	Busulphan	Lympho-sarcoma	Biopsy	Not stated	Generalized lymphadenopathy	1 month
Lüscher (1960)	80	CML	Busulphan	Reticulum cell sarcoma	Autopsy	4 years	Lymphadenopathy	3 months
Belotipetskaya & Gets (1960)	22	CML	'Cytotoxics'	Reticulo-sarcoma	Biopsy	3 years	Lymphadenopathy	Not stated
Howell & Whitfield (1963)	44	CML	Busulphan	Lympho-sarcoma	Biopsy	2 years	Generalized lymphadenopathy	2 months
Howell & Whitfield (1963)	73	CML	Demecolcine and busulphan	Lympho-sarcoma	Necropsy	2 years	Pericarditis Pelvic mass and skin nodules	1 week
Kurai & Papp (1965)	42	CML	—	Lympho-sarcoma	Autopsy	Coincident	Pancoast syndrome	—
Wilson & Van Slyck (1966)	54	Lymphosarcoma	—	CML	Biopsy	2 years	Lymphadenopathy	—
Josephs <i>et al.</i> (1966)	41	CML	Radiotherapy, urethane, thiotepa	Hodgkin's sarcoma	Biopsy	5 years	Soft tissue swellings	4 months
Josephs <i>et al.</i> (1966)	50	CML	Busulphan	Reticulum cell sarcoma	Biopsy	11 months	Lymphadenopathy	4 weeks
Present case, 1966	54	CML	Busulphan	Lympho-sarcoma	1. Aspiration 2. Biopsy	3 years	Generalized lymphadenopathy	

complicated by monocytic leukaemia (Craven, 1936). Usually the diagnosis of chronic myeloid leukaemia has been established prior to recognition of the complicating disease, but in the case of Wilson & Van Slyck, a 54-year-old man, lymphosarcoma occurred 2 years before chronic myeloid leukaemia was detected (see Table 1).

Clinically the development of the second disease usually has been detected by lymphadenopathy—which occurred in the present case—although soft tissue masses also occurred in some of the cases referred to. Lymphadenopathy, however, is a typical finding in the terminal illness of chronic myeloid leukaemia when it may be sudden and accompanied by fever and splenomegaly (Morrow *et al.*, 1965). The peripheral blood does not always show the characteristics of acute leukaemia at this time, although this is the usual finding. Lymphadenopathy in chronic myeloid leukaemia is said to be rare (Dameshek & Gunz, 1964) but that it may occur, and that it may indicate a different disease process, is noted by Hayhoe (1960). When lymphadenopathy is found a rapidly progressive course of the leukaemic process has been anticipated (Emile-Weil & Isch-Wall, 1930; Scott, 1957). Clearly it is impossible to differentiate clinically the onset of the terminal phase of chronic myeloid leukaemia from the development of a complicating malignant lymphoma and some form of microscopic examination of the enlarged nodes is indicated. In the present case, as in that of Konecni, Andrejevic & Stosic (1957), needle aspirates yielded cytologically diagnostic material, which was later confirmed by routine histological methods. At necropsy the findings were those of chronic myeloid leukaemia only—the cervical nodes having been shrunken by radiotherapy. The diagnosis of two disorders of this type presents some difficulties; lymph nodes showing apparently typical changes of reticulum cell sarcoma may yield Ph_1 positive cells (Carbone, 1966) and extramedullary tumours which resemble reticulum cell sarcoma may occur in states of myeloid metaplasia (Lieberman, Rosvall & Ley, 1965). In some cases the progression has shown cytological features of 'la remontée cellulaire évolutif' described by Bessis (e.g. Introzzi, 1955; Konecni *et al.*, 1957).

Both radiotherapy and alkylating agents are cytotoxic, mutagenic and carcinogenic, and it may be significant that all recorded cases had received one or other (sometimes mixed) forms of treatment. It has been postulated that myeloid proliferation might be partially controlled in these cases and any stimulus to abnormal

proliferation therefore allowed to act more effectively on lymphoid tissues (Howell & Whitfield, 1963). Such a sequence of events could be interpreted as support for the lymphoid origin of myeloid cells suggested by Maximow & Bloom (1948); this view also has the support of Yoffey *et al.* (1961) although disputed by Ham (1961). The coexistence of lymphosarcoma, myeloid leukaemia and myeloma in a 70-year-old man might be regarded similarly (Hollard *et al.* 1965). That two previous cases were reported from this centre suggests that this event may not be very rare, and indicates the need for critical assessment of lymphadenopathy arising in the course of chronic myeloid leukaemia.

When 'lymphoma' complicates chronic myeloid leukaemia the leukaemia usually has been of the Philadelphia-negative type (Wilson & Van Slyck, 1966). Repeated attempts in the present case failed to produce satisfactory metaphase plates and we therefore cannot comment on this particular aspect of the problem from personal experience.

In some cases of chronic myeloid leukaemia it has not been possible to demonstrate the Philadelphia abnormality (Tjio *et al.*, 1966) and such patients appear to have a relatively poor prognosis; there has also been a high incidence of prior radiotherapy in such cases (Tough *et al.*, 1962). It would seem useful to report the findings in all cases where lymphoma develops as the numbers are presently too small to allow any conclusions to be drawn concerning the role of the Philadelphia chromosome in this situation.

The interesting findings of Josephs, Zarafonitis & Durant (1966) in their case 2 (two cell lines, 46 (Ph_1 +) and 52 (Ph_1 +) with extra chromosomes in groups C and D) clearly needs further study. The occurrence of extra chromosomes of either Ph_1 type or group C type is well recognized but extra chromosomes in group D are a new finding and have not been seen so far as we are aware in direct cultures from malignant reticuloses.

The final consideration is whether such cases are to be regarded in any other way than examples of coincidence. The increasing numbers of observations suggest that this may not be the correct view but until much larger numbers are available for analysis it is not possible to arrive at any firm conclusion.

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