Leukemia in Burkitt’s Lymphoma

By R. A. Clift, D. H. Wright and Peter Clifford

BURKITT’S TUMOR is a lymphoma of childhood with characteristic clinical, anatomical, histologic and epidemiologic features. The clinical and anatomical features of this tumor syndrome were first fully described by Burkitt in 1958, when he associated the jaw tumors with multiple visceral tumors seen in children of the same age group. Undoubted cases of this syndrome are recorded in the case notes of Sir Albert Cook, Uganda’s first missionary doctor, at the beginning of this century. In Kenya this tumor constitutes 46 per cent of all malignancies diagnosed in children under the age of 14 years, and in Uganda it constitutes more than 50 per cent of all childhood cancers.

The most characteristic clinical feature of more than half the cases is involvement of one or more quadrants of the jaw by a rapidly growing osteolytic tumor. Tumors may also be found in the salivary glands, thyroid, heart, liver, kidneys, adrenals, retroperitoneum, gonads and long bones. It is not uncommon for involvement of all these sites to be found at post-mortem. Extra-dural spinal deposits causing vascular changes in the cord may result in paraplegia. In contrast to other types of lymphoma, involvement of the superficial lymph nodes is uncommon, and splenic involvement minimal. The clinical features have been described in detail by Burkitt and O’Conor.

The tumor grows rapidly and most untreated cases die within 6 months of seeking medical advice. It responds dramatically but often ephemerally to treatment with alkylating agents, and less consistently remissions may be obtained with antimetabolites. White has reported marked regression of a jaw tumor locally irradiated with Co60.

O’Conor and Davies reviewed the histology of this tumor and concluded that it was a lymphoma. Histologically it has a uniform pattern of sheets of immature lymphoid cells interspersed with non-malignant histiocytes which often assume a clear or vacuolated form giving the tumor a characteristic “Starry sky” appearance (fig. 1). In Giemsa- and Leishman-stained imprints of the tumor, the tumor cells resemble lymphoblasts. The narrow rim of deep blue staining cytoplasm usually contains numerous sudanophilic vacuoles. Histologically and cytologically the Burkitt tumor is always a poorly differ-
entiated lymphocytic lymphoma, characteristically containing a large number of clear or foamy non-malignant histiocytes. Recent histochemical studies by Wright support this classification and confirm the uniformity of histologic type.

Burkitt has investigated the epidemiology of this tumor syndrome. With the possible exception of New Guinea this tumor has not been reported outside the continent of Africa. It is not limited to any one racial group, cases having occurred in Asians and in a European child from Northern Rhodesia. The distribution of the tumor across tropical Africa appears to depend on temperature and rainfall and can be closely correlated with the distribution of certain arthropod vectors. This has led to the suggestion that this tumor may be induced by an arthropod-borne virus. The age incidence of the tumor and its multifocal nature lend support to this hypothesis.

Burkitt and O'Connor stated that they had not seen leukemia in association with this lymphoma, although O'Connor reported two cases with diffuse bone marrow involvement revealed at post-mortem, and in a previous publication O'Connor and Davies reported one patient who terminally developed evidence of leukemia in the peripheral blood. Stansfield examined the blood of 32 cases and the marrow of five histologically proven cases of this tumor and found no blood or marrow changes that could be considered leukemic. The low incidence of childhood leukemia in areas where the tumor occurs was reported by O'Connor and Davies who suggested that the reversed leukemia to lymphoma ratio might indicate a difference in the natural history of the lymphopoietic tumors in African children. This hypothesis has recently been
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expanded by Dalldorf who suggested that the Burkitt lymphoma might be an unusual manifestation of acute lymphoblastic leukemia of childhood.

Recently, leukemic manifestations were observed in four consecutive cases of Burkitt’s tumor admitted to the King George VI Hospital in Nairobi. One case developed a leukemic blood picture, and three cases developed aleukemic leukemia. These cases are the subjects of the following case reports.

CASE REPORTS

Case 1, 4363/62

A 12 year old African boy was referred from a Kenya hospital on June 19, 1962 with a 2-week history of swelling of the jaw. He had a huge, hard, fixed swelling of the mandible. There was no jaundice and the liver and spleen were not palpable.

A biopsy of the mandible showed infiltration by masses of small round cells with scanty cytoplasm. In some areas these were arranged in columns. There were scattered spaces containing foamy histiocytes with debris. Areas of necrosis and vascular granulation tissue were present throughout the specimen. The histologic picture was compatible with a diagnosis of lymphosarcoma but did not show the more usual pattern of a syncytium of immature lymphoid cells associated with Burkitt’s tumor syndrome. The kidneys could not be palpated but the blood urea nitrogen was 88 mg./100 ml. The peripheral blood picture was as follows: Hb 13.0 Gm./100 ml.; leukocytes 11,200 per cu. mm., with neutrophils 49 per cent, lymphocytes 40 per cent, monocytes 2 per cent, eosinophils 9 per cent. No abnormal cells were seen. Platelets were 220,000 per cu. mm.

The patient was given 3.0 mg./Kg. of nitrogen mustard (Mustine Hydrochloride) intravenously, the marrow and brain being protected by aortic occlusion and internal carotid occlusion under hypothermia. Full details of the chemotherapeutic measures employed will be reported elsewhere. As a result of this therapy, the tumor regressed completely and rapidly, although there was some persistent irregularity of the mandible. As tumor involvement elsewhere in the body was not apparent, a mandibulectomy was performed on August 8th. The child made satisfactory progress until September 15th when a conjunctival hemorrhage developed in the right eye. A blood count taken on September 15th showed Hb 8.2 Gm./100 ml.; leukocytes 18,000 per cu. mm., with neutrophils 9 per cent, lymphocytes 31 per cent, monocytes 1 per cent, myelocytes 2 per cent, lymphoblasts 57 per cent. Large numbers of smudge cells were present. Platelets were 30,000 per cu. mm. A marrow aspiration was contemplated but the child’s condition deteriorated rapidly and he died on September 18th before it could be performed.

Autopsy report: Tumor was present at the site of the mandibulectomy. Tumor deposits were found in the heart, para-aortic nodes and mesentry, liver, kidneys and adrenals. Although the tumor distribution in the kidneys was nodular, the liver showed a diffuse portal infiltrate characteristic of lymphatic leukemia. Histologic examination of the solid tumors in the kidney revealed sheets of immature lymphoid cells, giving the characteristic “starry sky” appearance associated with Burkitt’s tumor syndrome.

Case 2, 4203/62

A 6 year old Arab boy (fig. 2) was admitted on June 12th 1962 from the island of Zanzibar with a huge fixed swelling of the right maxilla.

A biopsy was performed. The specimen consisted of a non-ulcerated skin nodule covered with normal squamous epithelium. The subcutaneous tissues were extensively infiltrated with small round cells possessing scanty cytoplasm. These were arranged as a syncytium sprinkled with spaces containing histiocytes and debris. Histologic appearances were compatible with a diagnosis of lymphosarcoma.

Marrow aspiration revealed no abnormality and the blood picture was as follows: Hb
Fig. 2.—Arab child with lymphoma showing tumor of maxilla.

9.4 Gm./100 ml.; leukocytes 7,000 per cu. mm., with neutrophils 52 per cent, lymphocytes 38 per cent, monocytes 4 per cent, eosinophils 6 per cent. No abnormal cells were seen. Platelets were 360,000 per cu. mm. No tumor involvement could be demonstrated in other parts of the body. It was decided to treat this patient with the therapeutic regimen we use for acute leukemia. He was therefore given 6-mercaptopurine 2.5 mg./Kg. and prednisone 40 mg. daily from June 25th to July 10th. This treatment produced no regression of the tumor, which continued to grow rapidly. The dose of 6-mercaptopurine was therefore increased to 5 mg./Kg. per day on July 10th and further increased to 10 mg. Kg. on July 22nd. By July 28th the tumor was so large and was growing so exuberantly that the antimetabolite therapy was discontinued and the child was given nitrogen mustard (Mustine Hydrochloride) 1.0 mg. Kg. intravenously in two equal doses each of 0.5 mg./Kg. on July 28th and 29th. This initiated a marked regression of the tumor.

On September 1st the child developed chicken pox and it was not possible to administer further cytotoxic agents until October 16th by which time the tumor had again increased considerably in size and was now fungating into the mouth.

A further course of nitrogen mustard was administered (two injections each of 0.5 mg./Kg.) and again this caused a dramatic regression of the tumor. By November 11th the platelet count had fallen to 21,000 per cu. mm. and it was thought that this was due to hematologic toxicity from the nitrogen mustard. On the same day a marrow aspiration was made from the right iliac crest. The normal marrow was completely replaced by lymphoblasts (fig. 3). Large numbers of smudge cells were present, and the lymphoblasts had a characteristic morphology. The nucleus was round, oval or reniform and contained one to five indistinct nucleoli. The cytoplasm was narrow, staining dark blue with a perinuclear halo and containing numerous clear vacuoles.
Marrow aspirations were performed on the left iliac crest and the sternum to exclude the possibility that the first puncture had entered a localized tumor deposit. These marrows were also leukemic. A most careful search of the peripheral blood at this time revealed less than 0.1 per cent lymphoblasts with the characteristic morphology observed in the marrow. The leukocytes were 6,500 per cu. mm., with neutrophils 61 per cent, lymphocytes 36 per cent and eosinophils 3 per cent. The patient was treated with 6-mercaptopurine 2.5 mg./Kg. and 40 mg. prednisone daily, but his condition continued to deteriorate and he died on November 19th. Religious reasons prevented permission being obtained for an autopsy.

Case 3, 7891/62

A 6 year old African boy was admitted from a Kenya hospital with a large, hard swelling of the right maxilla. Multiple nodules were present in the thyroid but involvement of other organs was not detected. A biopsy of the maxilla on November 5th demonstrated clearly the familiar picture of a syncytium of cells interspersed with spaces containing histiocytes with debris, which we associate with the Burkitt's tumor syndrome.

An iliac crest marrow aspiration on the same day revealed complete replacement of normal marrow elements by lymphoblasts. Aspiration of the contralateral iliac crest and sternum showed the same leukemic picture. Examination of the blood showed Hb 10.5 Gm./100 ml.; leukocytes 12,000 per cu. mm., with neutrophils 49 per cent, lymphocytes 46 per cent, monocytes 5 per cent. Platelets were 340,000 per cu. mm. A careful search, however, revealed very scanty (less than 0.1 per cent) characteristic lymphoblasts.

Treatment with 6-mercaptopurine 2.5 mg. Kg. and prednisone 40 mg. daily was initiated immediately. This produced no response and edema of both upper eyelids developed. On November 22nd, ascites was noticed and the dosage of 6-mercaptopurine was increased to 5.0 mg./Kg. daily. On December 1st, the peri-orbital edema started to subside and the tumor to regress but a marrow aspiration the following day showed no remission of the leukemia. The peripheral blood remained aleukemic until his death on December 8th.

Autopsy: Tumor was present in the right maxilla, thyroid, para-aortic nodes, adrenals and liver.
A 3 year old African boy was admitted from Tanganyika on October 31st 1962 with a 4-month history of swelling of the left side of the face. He had a huge growth of the left mandible and maxilla. The nose was obliterated by the growth and there was proptosis and chemosis of the left eye. The liver and spleen were not palpated and involvement of other organ systems could not be detected. There was obstruction to the airway necessitating an emergency tracheostomy and the child’s condition was so serious that biopsy was not attempted and treatment was initiated on a clinical diagnosis of Burkitt’s lymphoma.

A total dose of 1 mg./Kg. of nitrogen mustard was given intravenously in two injections on November 3rd and 6th. The blood picture on November 3rd was Hb 9.1 Gm./100 ml.; leukocytes 5,200 per cu. mm., with neutrophils 64 per cent, lymphocytes 33 per cent, monocytes 3 per cent. Platelets were 180,000 per cu. mm. No abnormal cells were detected. An iliac crest marrow aspiration on November 17th revealed a hypoplasia of all elements (probably the result of chemotherapy) but no suggestion of leukemia.

The tumor regressed markedly but by November 22nd had started to grow rapidly again and a course of Melphalan 2.0 mg. Kg. was given. This caused no tumor regression. Marrow aspiration from both iliac crests and the sternum on December 2nd revealed hypoplasia of all marrow elements and no evidence of leukemia.

On December 4th, 1.0 mg./Kg. nitrogen mustard was given intravenously but the tumor continued to increase in size. Multiple marrow aspirations on December 15th showed almost complete replacement of normal marrow by lymphoblasts. A biopsy of the maxilla performed on the same day confirmed the clinical diagnosis of lymphoma. The specimen was a skin nodule covered with normal squamous epithelium. The dermis was replaced by sheets and columns of small round cells with scanty cytoplasm, and the picture was compatible with a diagnosis of lymphosarcoma.

The patient’s condition deteriorated rapidly and he died on January 2nd 1963.

**DISCUSSION**

During the past 3 years more than 60 cases of Burkitt’s lymphoma have been treated in the King George VI Hospital, Nairobi. Radiotherapy is not available and the very rapid progress of the tumor has dictated a vigorous chemotherapeutic approach using a variety of cytotoxic agents. This policy has necessarily resulted in numerous marrow investigations in this condition, but leukemia has not previously been noted. However, marrow studies undertaken for the control of cancer chemotherapy are not ideally suited to a study of the incidence of leukemic transformation, as many of the specimens are taken when the marrow is suffering the attrition inevitable in vigorous therapy with cytotoxic agents. Our previous policy for marrow sampling in connection with chemotherapy would have revealed only one of the above four cases of leukemia. A fall in the number of platelets associated with the development of leukemia may be false attributed to the influence of chemotherapy. Only one of the above cases had an easily recognized leukemic peripheral blood picture.

It is noteworthy that two of our cases died within 7 days of the diagnosis of leukemia and the other two died after 18 and 33 days. This indicates that the development of leukemia may be a terminal event in the natural history of the disease. O’Conor and Davies noted it as a terminal event in one case.

From a semantic point of view it is important to consider the nature of the change from solid tumor to leukemia. Burkitt’s lymphoma often involves bone
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Fig. 4.—Impression preparation from solid tumor in Burkitt's lymphoma.

at an early stage of the disease. These localized bone tumors may grow to a very large size by local extension without producing a leukemic marrow. We have tried to find the site in which the jaw tumor arises. It has proved difficult to locate the exact site or sites of origin but by a process of exclusion we feel that it probably arises within the marrow of the jaw. In the leukemias reported above, multiple marrow aspirations from widely separate sites have revealed the completeness of the marrow transformation. Radiography in these cases has not revealed bone changes similar to those present at the site of the solid tumors. The serial marrow aspirations from multiple sites in Case 4 suggest that the leukemic transformation occurs with great rapidity. These cases, then, probably do not represent solid tumor extension within the marrow cavity but may indicate a change in the nature of the tumor. In Cases 1, 2 and 4 reported above, this change may well have been induced or hastened by the previous chemotherapy. Case 3 had not been treated when the leukemia was diagnosed.

The constancy of the cell type in each of the four cases is of some interest. Wright has already noted the uniformity of the cell type in impression preparations made from biopsies of Burkitt's lymphoma (fig. 4). This cell is indistinguishable from that present in the marrows and peripheral blood of the leukemic patients, and no detectable cellular transformation seems necessary for the development of the leukemic state. This cell does not have any unique features and similar cells may be seen in classical lymphoblastic leukemia.

The finding of leukemia in these cases might lend support to Dalldorf's speculation that the Burkitt tumor is an unusual manifestation of acute lymphoblastic leukemia of childhood. However, this hypothesis does not take
into account the low incidence of both Burkitt's tumor and acute lymphoblastic leukemia in the highland regions of East Africa and also in South Africa.16 Geographic variations in the incidence of leukemia are considerable and have been reviewed by MacMahon.17

The evidence available at present favors the hypothesis that the Burkitt tumor forms a unique tumor syndrome probably induced by an arthropod-borne virus. If a comparison is made with virus-induced leukemia of experimental animals, the immediate post-natal period would be the most critical time for exposure to the responsible virus.15 The seasonal variation in rainfall in most parts of Africa with a corresponding variation in mosquito density and spread of arthropod-borne viruses suggests that the incidence of lymphoma should be analyzed in terms of the month of birth. This investigation is now in progress.

SUMMARY

1. Four cases of Burkitt’s tumor with terminal lymphoblastic leukemia are recorded.
2. The lymphomatous nature of the disease is thus confirmed.
3. The relationship of Burkitt’s tumor to classical lymphoblastic leukemia and its possible viral etiology are discussed.

SUMMARIO IN INTERLINGUA

Es registrate quatro casos de tumor de Burkitt con terminal leucemia lymphoblastic.
Le natura lymphomatose del morbo es assi confirmate.
Es discutite le relation de tumor de Burkitt con classic leucemia lymphoblastic e su possibile etiologia viral.

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