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Acute Burkitt's Leukemia: Case Report and Literature Review

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The occurrence of leukemia in Burkitt's lymphoma, with or without visceral or nodal tumefaction is uncommon, and its initial presentation as leukemia is even more unusual. Because it has a poor chemotherapeutic response and a grave prognosis, it is important to recognize this unusual leukemia correctly. Our report describes the clinical and pathologic findings of Burkitt's lymphoma cell leukemia in a five-year-old white boy who presented with abdominal distension, hepatosplenomegaly, and lymphadenopathy. Blood examination revealed normocytic normochromic

anemia, erythroblastosis, slight leukocytosis, and the presence of numerous (24%) blasts. A diagnosis of Burkitt's lymphoma was established on the basis of morphologic, cytochemical, and immunologic studies performed on the blasts. When the chemotherapy protocol for the lymphoma was administered, the patient responded well initially but suffered uric acid nephropathy, which was successfully treated. However, within two weeks he had a rapid relapse of leukemia and died four months after admission.

Burkitt's lymphoma is a bone tumor of the jaw usually found in Africa (1,2). Although it has been known to involve organs other than the jaw, the incidence of bone marrow involvement is still not as common as with other non-Hodgkin's lymphomas (3). In the American variety of Burkitt's lymphoma, bone marrow involvement has been reported in 8% to 30% of cases (4-6). In rare instances, leukemia may occur during the course of the disease, usually as a terminal event.

Very few cases have been reported in which this disease presented initially as true leukemia (7-12), and fewer have been studied in detail (8,10). We report such a case of leukemia with its characteristic clinical, histologic, and immunological features.

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Case Report

A five-year-old white boy was admitted with complaints of abdominal pain associated with increasing abdominal distention and vomiting that had lasted for one week. His past medical history and family history were unremarkable. Physical examination revealed a pale child with generalized lymphadenopathy. Chest examination revealed decreased breath sounds and dullness to percussion in both bases. The heart rate was 150/min with regular rhythm. Blood pressure was 120/60. His abdomen was distended with a prominent fluid wave. Spleen was enlarged to 4 cm below the left costal margin, and the liver was palpable at the right costal margin.

The laboratory findings were hemoglobin 10.5 gm%, hematocrit 32.3%, white cell count $19,600 \times 10^3$, platelets $286,000/\text{mm}^3$, white cell differential count 44% PMNs, 8% bands, 4% metamyelocytes, 3% myelocytes, 2% promyelocytes, 5% monocytes, 10% lymphocytes, and 24% blasts with basophilic cytoplasm containing multiple vacuoles (Fig. 1). The only other abnormal laboratory findings at this time were an elevated serum lactic dehydrogenase (LDH) of 2,480 U/L and an increased erythrocyte sedimentation rate of 22 mm/hr.

The chest radiograph revealed bilateral pleural effusion. A computerized axial tomogram of the abdomen demonstrated enlarged lymph nodes along the aorta and a mass in

the area of the terminal ileum. Also seen was right-sided hydronephrosis, possibly secondary to partial obstruction at the ureteropelvic junction.

A biopsy of the supraclavicular lymph node was performed, and when the specimen was stained (H & E stain) and examined, partial effacement of normal lymphoid architecture was seen due to a monotonous but "starry

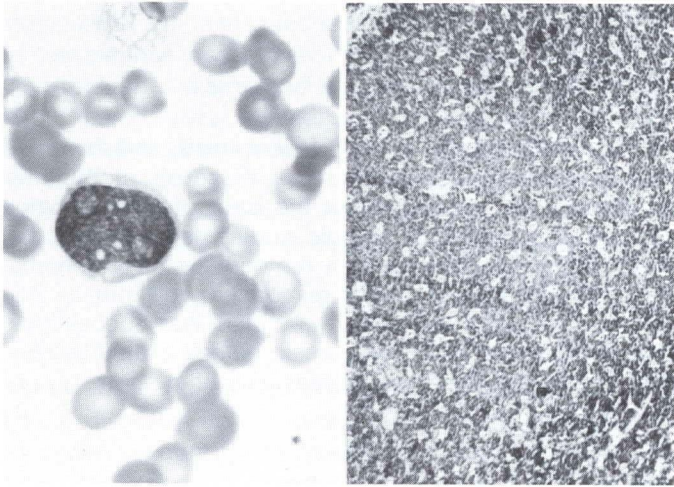


Fig. 1: Left

Burkitt's leukemia cell in peripheral blood smear. Leishman stain (1000X).

Fig. 2: Right

Section of lymph node involved by the neoplasm showing characteristic starry sky pattern. H & E stain (63X).

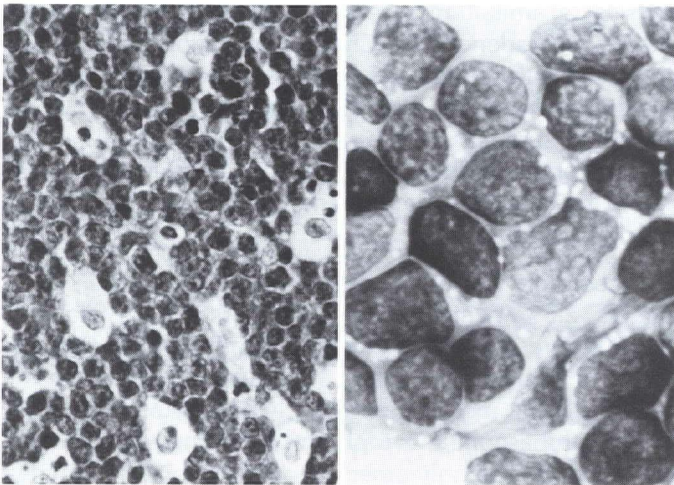


Fig. 3: Left

Higher magnification of lymph node section showing monomorphic population of undifferentiated blasts interspersed with benign phagocytic histiocytes. H & E stain (400X).

Fig. 4: Right

Imprints from lymph node showing Burkitt's tumor cells. Leishman stain (1000X).

sky" infiltrate composed of undifferentiated blast cells and phagocytic, benign histiocytes (Figs. 2,3). In the imprints the blasts had fairly round, noncleaved nuclei surrounded by a rim of deeply basophilic and vacuolated cytoplasm (Fig. 4). The nuclear chromatin was fine with two to four small to medium-sized nucleoli. The cells produced significant pyroninophilia with methyl green pyronin stain and stained negatively with para-aminosalicylic acid (PAS). An iliac bone marrow aspirate (Fig. 5) and biopsy indicated massive infiltration of the marrow by the undifferentiated blasts. Thoracentesis yielded serosanguinous fluid, with 35% lymphoblasts. Cerebrospinal fluid analysis was nondiagnostic.



Fig. 5

Bone marrow smear showing extensive infiltration with Burkitt's tumor cells. Leishman stain (1000X).

On the basis of the above findings, acute Burkitt's lymphoma cell leukemia was diagnosed. A modified LSA₂L₂ protocol for pediatric lymphomas was prescribed for the patient, and chemotherapy was initiated with cytoxan (1200 mgm/M² IV on day 1), vincristine (1.5 mgm/M² IV weekly times four doses), prednisone (60 mgm/M² in four divided doses for 28 days), methotrexate (6.25 mgm/M² IT weekly times four doses), and daunomyecin (60 mgm/M² IV on two successive days between the second and third vincristine injections). He also received allopurinol. However, when the boy's blood urea nitrogen (90 mg/dl) and uric acid (21 mg/dl) became markedly elevated, it was apparent that he was developing uric acid nephropathy and renal failure due to the rapid breakdown of his tumor. He was also hypertensive and developed alpha streptococcal septicemia. The uric acid nephropathy was successfully treated with intravenous fluids, allopurinol, diamox, and alkalization of urine. His hypertension was controlled well with thiazide and aprizoline. Ticarcillin and tobramycin were instituted to treat the sepsis. He was discharged on maintenance doses of prednisone.

Acute Burkitt's Leukemia

TABLE I
Clinical and Laboratory Features of
Cases Diagnosed as Acute Burkitt's Cell Leukemia

Case	Age	Sex	Presenting Features	Lymph Nodes	Spleen	Liver	Other	Bone Marrow Morphology	Hb G/dl	WBC Count with % Blasts in Peripheral Blood	Cell Marker Studies	Abnormal Bio-chemical Findings	E.B. Virus Studies
1 ⁽⁷⁾	17	F	Hematuria, Nuchal ache, Weight loss, Abdominal, chest pain	+++	++	++	—	90% blasts	10	WBC 27000/mm ³ Blasts, 65%	not done	LDH, SGOT, BUN, Uric acid	Unremarkable
2 ⁽⁸⁾	8	M	Swelling cheeks, proptosis, bleeding from gums, in stools	++	++	++	Facial swelling	100% blasts	4.5	WBC 59,700/dl Numerous blasts	not done	—	Not elevated
3 ⁽⁹⁾	14	M	Neck swelling, pain in jaw with loosening of teeth, bleeding gums	++	+	+	Tumor, left upper lid	Sheets of blasts	7.2	WBC 5800/mm ³ scanty blasts	not done	BUN	Not done
4 ⁽¹⁰⁾	14	F	Fever, abdominal pain	—	++	+	Petechiae, enlarged ovary involved by lymphoma	88% blasts	10.2	WBC 14,200/mm ³ Blasts, 22%	Suggestive of non-B non-T possibly null	SGOT, LDH, BUN, Uric acid	Elevated
5 ⁽¹¹⁾	5	M	Anorexia, anemia, abdominal swelling and pain	++	+	++	Abdominal masses	100% blasts	9.6	WBC 25,299/ul Blasts, 9%	not done	Uric acid, total protein	Not done
6 ⁽¹²⁾	12½	F	Acute abdominal pain	+++	—	—	Lymphomatous tumor in ileum, mesentery	Massive infiltration with blast cells	12.5	WBC 16,700/mm ³ Blasts, 30%	IgM kappa in 60% of blasts	Uric acid, SGOT, alkaline phosphatase	Normal
7 ⁽¹²⁾	15	F	Fever, facial swelling, bleeding gums	++	++	++	Breast masses, maxillary swelling, proptosis	Massive infiltration with blast cells	12	WBC 33,000/mm ³ Blasts, 80%	IgM kappa in 90% of blasts	LDH	Normal
8 our case	5	M	Vomiting, abdominal pain	++	++	+	Mass in terminal ileum, ureter; pleural effusion	100% blasts	10.5	WBC 19,600 X 10 ³ Blasts, 24% to 50%	IgM kappa, IgD	LDH	Normal

When the patient was discharged, his serum LDH was 11 U/L. Both uric acid and blood urea nitrogen were normal, and no blasts were seen in the peripheral blood smear. His abdominal girth was significantly reduced; a CAT scan of the abdomen demonstrated a marked reduction in the size

of periaortic and ileocecal masses. A repeat bone marrow aspirate showed slight hypoplasia but no tumor. However, within two weeks of the patient's discharge, the peripheral blood examination revealed 50% blasts. Immunological marker studies indicated that monoclonal membrane-

TABLE II
Response to Therapy and Prognosis in Cases
Diagnosed as Acute Burkitt's Cell Leukemia

Case	Chemotherapy	Initial Response to Therapy	Duration of Remission	Mode of Relapse	Length of Survival	Terminal Autopsy Findings
1 ⁽⁷⁾	Vincristine, prednisone	Dramatic and complete	About 1 week	Blood and marrow CNS (positive CSF)	3 months	Massive hemorrhage, sepsis, generalized leukemic infiltrate
2 ⁽⁸⁾	Vincristine, cyclophosphamide prednisone	Poor, died four days after admission	—	—	4 days	Neoplastic involvement of jaws, orbits, marrow, liver, spleen, GI tract, lymph nodes
3 ⁽⁹⁾	Cyclophosphamide	Complete remission	20 days	Blood and marrow	4 months	Extensive marrow involvement with hepatosplenomegaly, lymphadenopathy
4 ⁽¹⁰⁾	Cyclophosphamide	Complete remission	6 months	Blood and marrow	7½ months	Sepsis, internal hemorrhage, renal failure; extensive neoplastic infiltrate in marrow and abdominal viscera
5 ⁽¹¹⁾	Vincristine, methotrexate, prednisolone	Complete remission	3 weeks	—	3 weeks	Leukopenia, bronchopneumonia
6 ⁽¹²⁾	Cyclophosphamide, vincristine, prednisone, methotrexate (intrathecal)	Complete remission	3 weeks	Blood and marrow Meningeal	6 months	Marrow and meningeal involvement, neutropenia and E. coli sepsis
7 ⁽¹²⁾	Cyclophosphamide, vincristine, prednisone, methotrexate	Complete remission	4 weeks	Meningeal leukemia	11 months	Diffuse neoplastic involvement of CNS
8 our case	Cytosan, vincristine, prednisone, methotrexate (intrathecal)	Complete remission	1 month	Blood and marrow	4 months	Massive marrow involvement by neoplasm, pneumonia, severe thrombocytopenia

bound IgM (kappa) immunoglobulin was present on 88% and IgD was present on 65% of the blasts. The patient was hospitalized again for chemotherapy, but he developed pneumonia as well as persistent thrombocytopenia that required several platelet transfusions. In spite of vigorous chemotherapy and supportive measures, his condition became worse, and he died four months after his disease had been first diagnosed. An autopsy was not performed.

Discussion

Burkitt's lymphoma is a well-defined neoplasm (1,2) and both African (2) and American (3,5) varieties have been studied. In the American subtype, extensive bone marrow involvement is more common (4-6), although leukemia as

a terminal phase is not common (4,5,13). Leukemia is not commonly the initial presenting event, and most such reports have originated outside the United States. Since Stevens, et al reported a case of Burkitt's cell leukemia in 1972 (7), only a few additional cases with the initial leukemic component have been reported (7-12). It is well recognized that almost 3% of the acute lymphoblastic leukemia cells have B-cell immunologic markers and possess cytoplasmic pyroninophilia and vacuolization. These patients do not have visceral and/or soft tissue involvement like that seen in Burkitt's lymphoma. Therefore, B-cell acute lymphocytic leukemia cases (14) should be separated from cases which have typical clinical and pathologic findings of Burkitt's lymphoma with a presenting leukemic component.

Acute Burkitt's Leukemia

The reported cases of Burkitt's leukemia (Tables I and II) are similar to the non-African and American Burkitt's lymphomas in their characteristic clinical presentation and multiple organ involvements. Abdominal organ involvement was most frequent. But unlike the lymphomas, seven of eight cases of leukemia presented with varying degrees of generalized lymphadenopathy. Bone marrow involvement in all cases was always massive, and the peripheral white cell count in most instances was significantly elevated. Chemotherapy produced a dramatic initial response in all cases except for one patient who lived only four days after admission. However, the remission in all cases was short-lived with relapse of leukemia and rapid death. The patients survived after relapse usually less than six months. Terminal or autopsy findings in seven of eight patients included widespread neoplastic organ infiltrates with associated sepsis and hemorrhage in some cases. The response and short survival of these patients is similar to that of most cases of American Burkitt's lymphoma where bone marrow was extensively involved. Epstein-Barr viral titers were usually normal or not significantly elevated in all but one patient (Tables I and II). This finding supports the contention of some authors (15) that the Epstein-Barr virus titers may be less significant in non-African Burkitt's leukemia and lymphoma than in the African variety.

Immunological studies have been performed in only a few cases of Burkitt's leukemia. In most cases, including ours, monoclonal surface immunoglobulins (usually IgM kappa) were consistently present. Presence of delta chains in our case is not surprising since these are produced by IgM-bearing normal or neoplastic lymphoid cells (14,16).

Cadman, et al (17) studied uric acid nephropathy that developed during effective chemotherapy in Burkitt's lymphoma and leukemia due to rapid cell lysis. As they indicated, a markedly elevated LDH forewarned us of this possibility, as did the clinically and morphologically extensive neoplastic infiltrates in our patient. We were thus able to successfully treat this aspect of the disease.

Conclusion

Cases of acute Burkitt's leukemia differ from the typical cases of B-cell acute lymphocytic leukemia (B-ALL) with massive multi-organ involvement. The associated clinical and pathologic findings of Burkitt's lymphoma do not occur in cases of B-ALL, although extensive marrow involvement, many blasts in the blood, and lymphadenopathy are common accompaniments. Burkitt's leukemia may represent a particularly aggressive form of B-lymphoblast malignancy which shows sudden, massive tumefaction and leukemia that is difficult to control with the commonly employed chemotherapy for Burkitt's lymphoma or childhood ALL. The few cases in which detailed immunological studies on the tumor cells have been performed demonstrated monoclonal B-cell markers.

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