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Malignant Lymphoma Resembling "Burkitt's Tumor" in Korea*

—Report of A Case—

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INTRODUCTION

Burkitt's tumor is a variant of malignant neoplasm of the hematopoietic system and is more specifically designated as malignant lymphoma, undifferentiated, Burkitt's type.[1, 27] In 1958, Burkitt[4] called attention to a remarkable prevalence, in equatorial Africa, of a round cell tumor that appeared predominantly in children between the ages of three and nine years, with predilection for the jaw in males and the ovaries in females. With subsequent investigations from many subspecialty fields, this type of neoplasm has become more apparent with following somewhat distinctive features: (1) An extremely high incidence in African children(median age of 5 years), so high that the tumors comprised 50 per cent of all malignant tumors in this age group in this area. (2) An apparently limited geographical distribution across the middle of Africa, involving principally the Belgian Congo, Uganda, Kenya and British East Africa, with some scattered cases in French West Africa and French Equatorial Africa.[5, 6] This relatively humid tropical climate (rainfall over 20 inches per year) suggested the possibility of a specific arthropod vector and raised the further possibility that the lymphoma might be caused by a transmissible, possibly viral agent requiring specific temperatures and humidity modalities for the survival of insect vector.[4] (3) An unusual anatomic distribution affecting principally the jaw and abdominal region. (4) The absence of leukemic manifestions in all cases, even in the advanced stages of the disease, giving rise sometimes to the designation "non-leukemic lymphoma".[6]

Reports of strikingly similar lesions in young children in the United States and in other countries outside tropical regions have recently appeared.[2, 3, 9, 10, 16-18, 21-24, 29, 30, 33] As indicated by O'Conor et al,[24] this tumor is not peculiar to Africa, and, rather, it represents a striking variation in expected incidence of non-leukemic childhood lymphoma, a disease relatively uncommon elsewhere[23]. This is interpreted as illustrating, first, that the manifestations of lymphosarcoma in children differ from that in adults and, second, that childhood lymphosarcoma in the U.S.A. is similar to that in Africa in age distribution, clinical manifestations, course and histological appearance.[10] And the latter concept has been

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supported partly by the dramatic response to Cyclophosphamide[7], immunologic deficiencies of antibody production and immunoglobulin level[7], and high titers of anti-herpes-like virus antibody in both African and American patients with Burkitt's tumor[7, 26]. The unusually high incidence of the disease in Africa over a particular geographical area, its predilection for the bones of jaw and face and rarity of leukemic transformation, may reflect an altered host susceptibility in children in that area of Africa, apart from environmental factors.[24]

Because of histological similarites, however, many of cases featuring stem cell or undifferentiated lymphomas of extranodal origin have been discussed along the line of Burkitt's tumor. But it has to be established only after cytologic study of imprint of fresh tumor or tumor cells in fluid, or by use of special stains.[32]

The case presented here documents a malignant lymphoma of undifferentiated type resembling Burkitt's tumor in non-African areas. Morphological features which are helpful in recognition of this disease are detailed.

PRESENTATION OF CASE

First Admission

A two years and two months old Korean male infant was admitted to Seoul National University Hospital for the evaluation of anorexia and abdominal distention for the first time on October 12, 1970.

He had been in good health until one month prior to admission, when his monther noticed swollen left cheek. The patient visited a dental clinic where extraction of tooth was done under the impression of odontitis. After extraction, swelling of left cheek persisted and x-ray film of skull revealed irregular erosion of left maxilla(Fig. 1). Biopsy from left gum was performed. Soonafter, cobalt therapy was started at the Radiological Research Institute attached to Office of Atomic Energy. During cobalt therapy, blood transfusion was necessary for the correction of anemia. Further detailed history of clinical course could not be obtainable. Ten days prior to admission URI-like symptoms developed, being followed by anorexia and abdominal distention. One day before entry urine volume became markedly reduced near to anuric state. Family history was unrevealing.

Physical examination on admission revealed a moderately developed and moderately nourished male infant in chronic distress but with clear consciousness. Blood pressure was 100/50 mm Hg. and body temperature 36°C. Sclera was slightly icteric and left pupil was miotic. Prompt light reflex was noted in the right side but questionable in the left. Left cheek and nose were swollen and showed dark brownish discoloration of the skin. Chest was symmetric; neither rales nor murmurs were audible on auscultation. The liver was palpable 3 finger-breaths below the right costal margin, but other visceromegaly or peripheral lymphadenopathy was not manifest.

Laboratory examination on admission revealed hemoglobin of 12.0 gm/dL; hematocrit 39%; W.B.C. 10,100/mm^3 with 1% of meta., stab. 2%, seg. 61%, lympho. 30%, mono. 1%, eosino. 4%. E.S.R. was 3 mm/hr. Blood chemistry revealed total bilirubin of 6.00mg% with direct bilirubin 3.75 mg%; T.T.T. 5.7 unit; toal protein of 6.3gm/dL with albumin 4.1gm/dL; alkaline phosphatase 22.0 unit; s-GOT 450 unit; s-GPT 430 unit; Na 140 mEq/L; K 4.0 mEq/L; and Cl 102 mEq/L. Urinalysis showed specific gravity of 1.017, albumin (−); sugar (−); urobilinogen (±); bilirubin (+) and no R.B.C.

X-ray film of chest demonstrated pulmonary streaky and patchy densities suggesting pneumonitis, and upper G-I series showed huge

filling defect at pyloric antrum. But X-ray films of simple abdomen, small bowel series and I. V. P. were unremarkable.

During hospitalization 2mg/week of Vinblastin and 30 mg/day of prednisolone were given under the impression of acute viral hepatitis and malignant lymphoma. The clinical symptoms and signs were gradually improved and discharged on October 26, 1970.

Second admission:

On November 7, 1970, the patient was readmitted because of abdominal distention and oliguria, which developed 2 days prior to admission. Positive findings included dull consciousness, markedly distended abdomen without tenderness, and pitting edema in the extremities. Abdominal paracenthesis was done to reveal 50 cc. of yellowish transudate. During hospitalization intractable vomiting and abdominal distention persisted. He was going downhill course until he expired on November 13, 1970. Autopsy was not granted.

Pathologic Findings:

The specimen submitted was two pieces of grayish white, friable and partly fibrotic tissue with suggestive epidermoid covering, the larger one of which measured 1. 2x 0. 5x 0. 4 cm.

Microscopically, the neoplasm was highly cellular, consisting entirely of immature or undifferentiated lymphoreticular cells permeating throughout the portions of fibrous tissue (Fig. 2, 3 and 4). Uniformly scattered throughout the neoplasm were non-neoplastic large histiocytes with active phagocytosis of cell debris, embedded within the above mentioned cells of undifferentiated lympho-reticular origin, representing so-called "starry sky" phenomenon. Reticulin deposit was scanty and encircled groups of tumor cells with uneven distribution. Individual tumor cells were much similar to so-called stem cells having vesicular chromatin distribution and prominent nucleoli as with basophilic cytoplasmic rims. But fat vacuole in the cytoplasm was not definitive.

Cytologic study on ascitic fluid disclosed many nucleated cells of lympho-reticular origin, varying from 10 to 25 μ in diameter. A moderate amount of intensely basophilic cytoplasm was present with a variable number of small vacuolization and perinuclear halo formation. Nuclei were round to oval with rare indentation or lobular configurations. Nuclear membrane was distinct and nuclear chromatin was coarsely reticulated and irregularly distributed. One to three nucleoli were discernible in each nucleus. Mitosis was frequently demonstrable.

DISCUSSION

Much of the confusion about the nature of the lymphoma in the Africa known as the "Burkitt' s tumor" is due to a lack of definition and to the semantic impasses encountered in the classification of tumors of the lymphoreticular system.[24] It is reinforced by a series of reports of similar cases from non-African countries. To some authors, the term "Burkitt's tumor" connoted a specific pathological entity restricted to Africa; to others, a clinical or clinicopathological syndrome; to still others any large malignant jaw tumor in a child; and, to apparently only a few, specific type of lymphoma seen everywhere but unusually common in Africa.[7] The predominant and characteristic cells in the presented case are undifferentiated lymphoreticular or primitive stem cells showing moderate nuclear and cytoplasmic variations interpretable either as biological differentiation to histiocytic or lymphocytic cell types. Macrophages are frequently interspersed amid the tumor cells so as to form a so-called "starry-sky" pattern. Al-

though a prominent histological feature, this pattern is not specific to or pathognomonic of Burkitt's tumor, often such a lesion can be demonstrated not infrequently in cases of malignant lymphomas arising either from lymph nodes or alimentary tract. A consideration of clinical and gross anatomical features is summarized, together with a description of the component cells of the tumor by which these cells can be characterized, and a discussion of differential diagnoses. [1, 6, 22]

Clinical Aspects and Gross Pathology

Although many clinical features of Burkitt's tumor particularly the anatomical presentation and distribution, tend to be characteristic, none is pathognomonic and a variety of malignant neoplasms have similar clinical manifestations. [1] In general, clinical and laboratory signs and symptoms are essentially related to the anatomical distribution of the tumor and to its impingement on vital structures.

In 1967 the WHO International Reference Center for the Histopathology of Leukemias and Other Neoplastic Conditions of the Hematopoietic Cells at Villejuif, reemphasized the importance of the proper and accurate definition of Burkitt's tumor, and the Organized Committee in collaboration with the International Agency for Research on Cancer recommended the following principal clinical and gross anatomical features needed for the diagnosis of Burkitt's tumor[1, 7]: (1) Predominantly a tumor of childhood; the disease, however, may occur in any age-group. (2) Rapid onset and rapidly fatal course in untreated cases. (3) Clinical presentation as a rapidly growing solid tumor or tumors which are predominantly extranodal. The disease is usually multifocal and widely disseminated, with involvement of one or more sites including: (a) abdominal and/or pelvic viscera, (b) retroperitoneal soft tissues, (c) facial bones and/or long bones, (d) thyroid gland, (e) salivary glands, (f) cental nervous system. [7] Retroperitoneal masses and discrete nodular involvement of the abdominal viscera are found in virtually all cases even when jaw tumors are the dominant manifestation. The kidneys, liver, gonads, and endocrine organs are frequently involved. [22, 31] Bilateral ovarian tumors in females at all ages are a particularly characteristic feature of the disease, as also are massive bilateral breast tumors in women of child-bearing age. Tumors in the spleen, mediastinum, and lungs are uncommon and rarely massive. Nodular deposits in the epicardium and myocardium are not infrequent.

There is conspicuous sparing of the peripheral lymph nodes in most cases but occasional patients may exhibit tumors in one or more of the peripheral chains. Unless pertinent histologic examination by necropsy is carried out, it is much skeptical in the presented case that nodal involvement was not manifest, but generalized peripheral lymphadenopathy due to tumor is rarely, if ever, found. Massive involvement of mediastinal nodes is likewise uncommon and primary tumor in the thymus has not yet been observed. Involvement of Waldeyer's ring is rare in cases of Burkitt's tumor in Africa but has been reported in the USA and England.

That the anatomic distribution of tumor as described is not peculiar to Africa but is characteristic of a significant proportion of childhood lymphomas everywhere has been emphasized previously. [28] The facial manifestation is unquestionably a distinctive one in Africa but localization of tumor at this site does not occur in all cases. In East Africa the reports indicate jaw or facial bone involvement in about 50% of cases while in West Africa it is found in only about 20 to 30 % of the cases. [11, 22]

Davies et al.[8] suggested that the African jaw may be a susceptible site and that any clinical or laboratory experience in Africa will provide many more examples of benign and malignant tumors of the jaw of all types than one would encounter elsewhere. Since malignant lymphoma is by far the most common tumor of childhood in East Africa, it is not surprising that frequent localization at the jaw of the African child is noted.

On the other hand, the frequency of jaw tumors in African cases is thought definitely to be related to age, the maximum incidence being at the age of 3 years and falling progressively thereafter. The apparent lower incidence of jaw tumors in cases reported from the United States may be due to a difference in the age incidence of Burkitt's tumor in the two continents or possibly to a greater susceptibility of the jaws of Africans to tumor growth.

Involvement of multiple quadrants of the jaw is common[6, 31] and, even when only one tumor is grossly evident, detailed pathological or radiological examination of the remaining quadrants usually reveals other small tumor foci. The tumors appear to begin as small osteolytic foci in the molar or premolar areas, coalescing to form large expanding tumors with displacement and loosening of the teeth. Involvement of bones other than the jaw is much less frequent but may occur as single or multiple tumors.

(4) Absence of significant leukemic manifestation in the peripheral blood. It is, however, of interest that non-African Burkitt's tumors often accompany leukemic permeation though the presenting infant is not the case. Although nodular tumor deposits are frequently seen in bones, diffuse infiltration or replacement of the bone marrow by Burkitt's tumor is uncommon except as a terminal or preterminal event and has not been reported in the absence of extensive disease elsewhere. Small numbers of tumor cells may be found in the peripheral blood in advanced cases but a significantly elevated white blood cell count due to those cells and frank leukemia has not been seen. A leukoerythroblastic reaction may be found in the peripheral blood in cases with bone marrow replacement.

Histopathology

Histologically, the neoplasm reflects a monotonous overgrowth of undifferentiated lymphoreticular cells with little variation in size and shape. Mitotic activity is high. Macrophages with abundant clear cytoplasm containing tumor cells or cell debris are almost invariably found scattered uniformly throughout the tumor, producing the characteristic "starry-sky" pattern. Supporting stroma and reticulin fiber distribution vary with the tissue involved. In large tumor masses reticulin is scanty and found as short thin strands between occasional groups of neoplastic cells.

The adhesiveness of the principal tumor cells varies considerably in different portions of the same section and depends largely on fixation. In well-fixed areas they are generally cohesive. Each cell, however, has a narrow rim of cytoplasm which, with hematoxylin and eosin stains, has a degree of amphophilia equivalent to that of plasma cells. With higher magnification the cells usually contain a few of the cytoplasmic vacuoles (lipid droplets) that are such a prominent feature of most imprint preparations. PAS reaction for glycogen is negative, in contrast, in as many as 70% of cases of acute lymphocytic leukemia, significant amount of PAS-positive material are found in the leukemic cells from bone marrow aspirates.[7]

The tumor cell nuclei are also very uniform

in size and approximate to that of the nuclei of scattered macrophages. They are unusually round but may occasionally be ovoid and show a slight indentation. The nuclear membrane is prominent. The coarsely reticulated chromatin is irregularly distributed in a relatively clear parachromatin. Nucleoli are prominent and are unusually 2 to 5 in number.

Lesions resembling Burkitt's tumor and differential diagnosis

Various types of poorly differentiated neoplasm, including metastatic carcinomas, rhabdomyosarcomas, neuroblastomas,[10] retinoblastomas,[30] granulosa-cell tumors and plasmacytomas have been mistakenly diagnosed as Burkitt's tumor.[1] However, the greatest difficulty in differential diagnosis is encountered with certain cases of acute leukemia and poorly differentiated malignant lymphomas.[7] The histological appearance of H & E-stained sections may be similar to that in Burkitt's tumor. In fact, the similarity may be so great that the differential diagnosis cannot be made on routinely stained sections and can be established only after study of imprints of fresh tumor or by the use of special stain.[1, 7]

In respect to histopathology the predominent cell types are considerably similar to those seen in malignant lymphoma, poorly differentiated or poorly differentiated histiocytic, type.[24, 27] Wright[32] suggested that the uniformity of cytological and histochemical pattern of the Burkitt's tumors as compared with ordinary malignant lymphoma does not justify the separation of the Burkitt's tumor into different histological types. It is partly supported by that several cell-line cultures have been established from the tumor cells of both African and Non-African Burkitt's tumors.[14, 15] From these cultures a number of viruses have been isolated, including vaccinia, herpes simplex, reovirus 3, and a herpes-like virus (HLV), originally detected by Epstein and his Workers[13–15] and designated as EB virus. The narrow age distribution suggests that widespread but subclinical infection may occur, with resulting immunologic protection from the majority of the population. To date intensive investigation has failed to confirm such an agent, but several recent provocative reports require close attention for viral etiology. Final demonstration of the mode of transmission, and confirmation of the EB or any other virus as the etiologic agent in Burkitt's tumor will depend on identifying the agent in an appropriate vector and on isolating it in an infectious form from affected patients. And, this will share an important role in proving the identity between those African and non-African types of Burkitt's tumor.

In Korea any single case of proven Burkitt's tumor was not as yet documented in the literature, although occasional cases having rather unusual anatomic localization of malignant lymphoma were noted.[20] Since this case showed peculiar histopathologic findings and anatomic localization compatible with Burkitt's tumor as the sporadic cases in the world, it is suggested that the "Burkitt's tumor" actually represents an expression of unusual incidence phenomenon with geographic delineations in Africa[24]. But in no way does this lessen the importance of the epidemiological observations which have been made in Africa and their possible etiological implications.

SUMMARY

A case of undifferentiated type of malignant lymphoma with histologic and clinical characteristics of "Burkitt's Tumor" in a 3 year-old Korean infant is presented, and is discussed along with assumption that this type of tumor is not limited to Africa and may occur in any part of the world.

—국문초록—

Burkitt 淋巴腫을 暗示케하는 未分化型 惡性 淋巴腫

—1 症 例 報 告—

서울大學校 醫科大學 病理學敎室

金勇一·安亘煥·徐廷翊·李尙國·李濟九

3歲된 韓國人 男兒의 上顎骨을 侵犯한 未分化型 惡性 淋巴腫으로서 그 病理組織學的 特徵과 臨床像이 *Burkitt* 淋巴腫을 暗示케하는 1例를 報告하고, *Burkitt* 淋巴腫의 一般形態學的 所見을 文獻的 考察과 더불어 要約記述하였다.

本 症例는 韓國人에서 처음으로 記載되었을뿐 아니라 아프리카 以外 他地域에서 드물게 報告된 症例와 함께 本腫瘍의 疫學的 意義 및 腫瘍發生에 새로운 面을 考慮케하였다.

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Fig. 1. Water's view of paranasal sinuses, demonstrating destruction of left maxillary sinus bone.

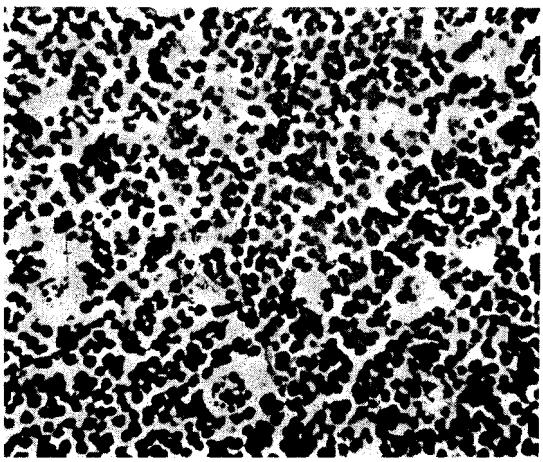

Fig. 2. Microphotograph of tumor tissue, illustrating monotonous overgrowth of undifferentiated cells simulating lymphoblasts with starry sky appearance. H-E. × 200.

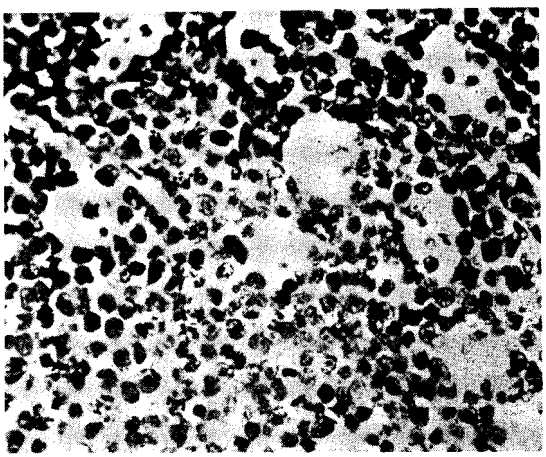

Fig. 3. High power view of Fig. 3, showing active phagocytosis of nuclear debris in non-neoplastic histiocytes. H-E. × 430.

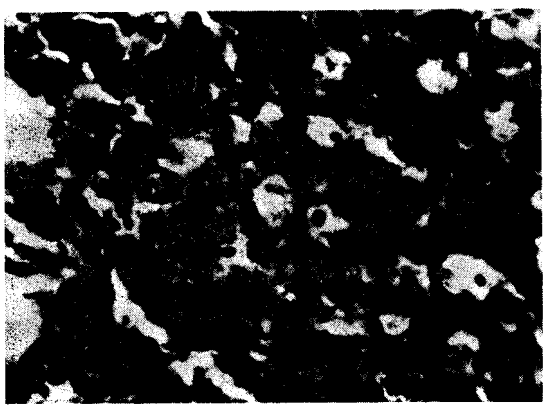

Fig. 4. More solid area of tumor cells with histologic features to suggest stem cell type of lymphoma. H-E, × 430.