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FATAL INFECTIOUS MONONUCLEOSIS IN A FAMILY*

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Two male siblings, one aged five and a half months (SB), and the other aged six months (VB), with fatal infectious mononucleosis phenotype of the X-linked lymphoproliferative syndrome, which resulted in the death of both infants, are presented. Both patients had been healthy, one until the age of five and a half months, and the other until the age of six months. Then, they developed a maculopapular rash, hepatosplenomegaly and lymphadenopathy. In one sibling, the serum IgG level was low, the IgM and IgA levels were high, and the proportion of E-rosette forming cells (E-RFC) and in vitro proliferative response to PHA were normal. In the other sibling, however, the serum IgG level was normal, the IgM and IgA levels were high and the stimulation index for proliferative response to PHA was reduced due to increased spontaneous blastogenesis. Anti-EBV antibodies were negative in both siblings, except for the IgM anti-VCA in V.B. A lymph node specimen could be studied in one infant and was found to be positive for the EBV genome. Postmortem histopathological findings included the absence of cortico-medullary differentiation and identifiable Hassal's corpuscles in the thymus and depletion of T-dependent regions of lymph nodes and spleen in V.B. Atypical mononuclear cell infiltration was detected in the portal areas of the postmortem liver biopsy in S.B. *Key words: fatal infectious mononucleosis, X-linked lymphoproliferative syndrome, thymic pathology.*

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X-linked lymphoproliferative syndrome (XLP), first reported by Purtilo et al[1], may occur as various phenotypes, i.e. chronic and fatal infectious mononucleosis (IM), acquired agammaglobulinemia, aplastic anemia, and B cell non-Hodgkin's lymphoma. Since its original description, many cases of this disease have been diagnosed in various countries[2,3]. We report two male siblings with fatal infectious mononucleosis phenotype who died, one at the age of six months, and the other at the age of six and a half months.

Case Reports

Case 1

S.B. was first seen at the age of five and a half months at the Hacettepe University Children's Hospital with complaints of high fever, generalized rash, diarrhea and vomiting.

He was healthy until about ten days prior to admission, when he developed a high fever, and then a skin rash. He was a well developed boy (weight 9.0 kg: height 71 cm). Physical examination revealed a febrile child with a maculopapular rash covering the entire body including the face and extremities, oral moniliasis, whitish spots on the tonsils, hepatosplenomegaly, and cervical lymphadenopathy (Table I). The fever remained high during hospitalization, and he developed melena. He died on the third day after his admission, about twenty days after onset of the illness.

TABLE I: Clinical Findings

SB	VB
AGE 5 1/2 MONTHS	AGE 6 MONTHS
W 9.0 kg, H 71 cm	W 9.0 kg, H 68 cm
FEVER	FEVER
ORAL MONILIASIS	MEMBRANE ON TONSILS
TONSILLITIS	AXILLARY LYMPHADENOPATHY
CERVICAL LYMPHADENOPATHY	HEPATOSPLENOMEGALY
HEPATOSPLENOMEGALY	MENINGEAL SIGNS AND
DIED ON THE 3rd HOSPITAL	JAUNDICE DEVELOPED
DAY, 20 DAYS AFTER ONSET	DIED ON THE 20TH HOSPITAL
OF ILLNESS	DAY, 30 DAYS AFTER ONSET
	OF ILLNESS

Case 2

V.B., the brother of S.B., was admitted to the hospital at the age of six months with the chief complaints of fever and skin rash. He was well developed and healthy until seven days prior to admission when he developed a skin rash which started from the shoulders and spread to the chest. Physical examination revealed

a child with a high fever, a maculopapular rash on the chest, abdomen, shoulders and upper arm, a membrane on the tonsils, axillary lymphadenopathy, and hepatosplenomegaly (Table I). His height was 68 cm and weight 9 kg. Since bacterial infection could not be ruled out, antibiotics, were started, and because of the low serum IgG level (<200 mg/dl), he was given gammaglobulin (1.8 mg/kg im). Despite this treatment, his condition gradually deteriorated, and he began to have seizures. Examination of the cerebrospinal fluid revealed mononucleated cells (55/mm^3), protein concentration of 85 mg/dl, and glucose 52 mg/dl. His hemoglobin level fell to 6 g/dl, and irradiated whole blood (10 cc/kg) was transfused. He developed jaundice and his condition deteriorated further. He died on the 20th day of hospitalization.

The parents of the siblings were unrelated and healthy. Two sisters, one seven years old and the other four years old were healthy. The second-born child in the family, a five-month old boy, had also died of an infectious disease with high fever (Fig. 1). Two aunts and four uncles on the paternal side are alive and healthy but a paternal uncle had died of pneumonia at the age of six months. Five aunts and six uncles on the maternal side had died of undetermined causes at ages ranging from 18 days to three and a half years.

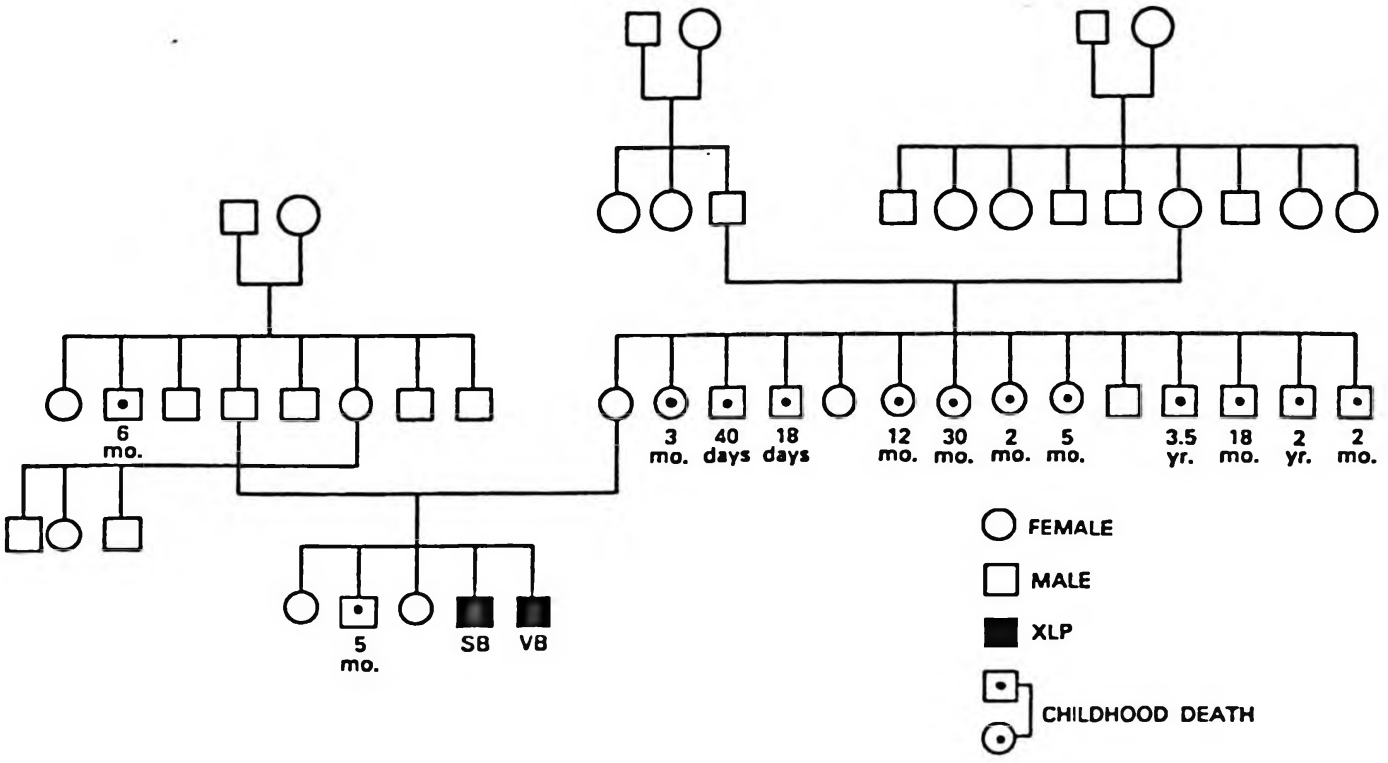

Fig. 1: Family Pedigree

Laboratory Findings :

Peripheral blood smears revealed atypical lymphocytosis and both patients developed neutropenia and thrombocytopenia (Table II). Case 1 had blast-like cells on the bone marrow smear. Because of the presence of atypical lymphocytes on the peripheral blood smear and blast-like cells in the bone marrow, acute lymphoblastic leukemia was initially considered.

TABLE II: Hematological Findings

	SB	VB
WBC/mm^3	16.600* 32.000**	16.800* 3.500** 4.100***
LYMPHOCYTES (%)	60* (15% ATYPICAL) 98**	75* (10% ATYPICAL) 86** 90***
NEUTROPHILS (%)	30* 2**	22* 6** 10***
MONOCYTES (%)	10*	3* 8**
THROMBOCYTES	ABUNDANT* REDUCED**	ABUNDANT* ABUNDANT** REDUCED***
BONE MARROW	COVERED WITH LYMPHOCYTES (BLAST-LIKE CELLS WERE PRESENT	LYMPHOCYTOSIS* HYPOCELLULAR EARLY** MYELOID ELEMENTS WERE INCREASED
LIVER	ATYPICAL MONONUCLEAR CELL INFILTRATION IN PORTAL AREAS (POSTMORTEM LIVER BIOPSY)	

* When first seen
** Ten days after admission
*** Twenty days after admission

Immunological findings and Epstein-Barr virus (EBV) serology are shown in Tables III and IV. Except for anti-VCA IgM in Case 2, both patients failed to mount anti-EBV antibodies. EBV genome determination was performed only in Case 2, and was found to be positive in the lymph node. The mother had high anti-VCA and anti-EA titers (EBV serology was studied with the kind assistance of the late Dr. W. Henle and the EBV genome determinations were performed by Dr. G. Klein).

TABLE III: Immunological Findings

	SB	VB
E-rosettes	49	69
Delayed type Skin tests	NT	Positive with PHA, Candida, SK-SD
Serum Ig's (mg/dl)		
IgG	630	< 200
IgM	485	425
IgA	115	93
In vitro response to PHA (cpm STI/UNSTI)	13916/10219 Control 8441/119	6685/66 Control 4670/40

TABLE IV: EBV SEROLOGY

		SB	VB	MOTHER	FATHER
VCA	IgM	1/10	1/20	–	–
	IgA	1/10	–	–	–
	IgG	1/10	1/10	1/6 640	1/1 160
EA	D	1/10	1/10	1/10	1/10
	R	1/10	1/10	1/40	1/10
EBNA		1/2	1/2	1/20	1/10
EBV GENOME		NOT TESTED	POSITIVE (IN THE LYMPH NODE)		

Histopathological Findings

Only a postmortem liver biopsy could be taken in Case 1 which revealed atypical mononuclear cell infiltration in the portal areas. But a complete postmortem examination in Case 2 revealed the absence of corticomedullary demarcation and

Hassal's corpuscles in the thymus (Fig. 2). Lymphocytes were depleted and there was an increase in perilobular fibrous tissue. Both the lymph nodes and white pulp of the spleen lacked lymphoid follicles and germinal centers (Figs. 3, 4). Periarteriolar lymphoid sheats were depleted of lymphocytes in the spleen. Punched out-like ulcerations were noted in the intestinal tract, and scattered

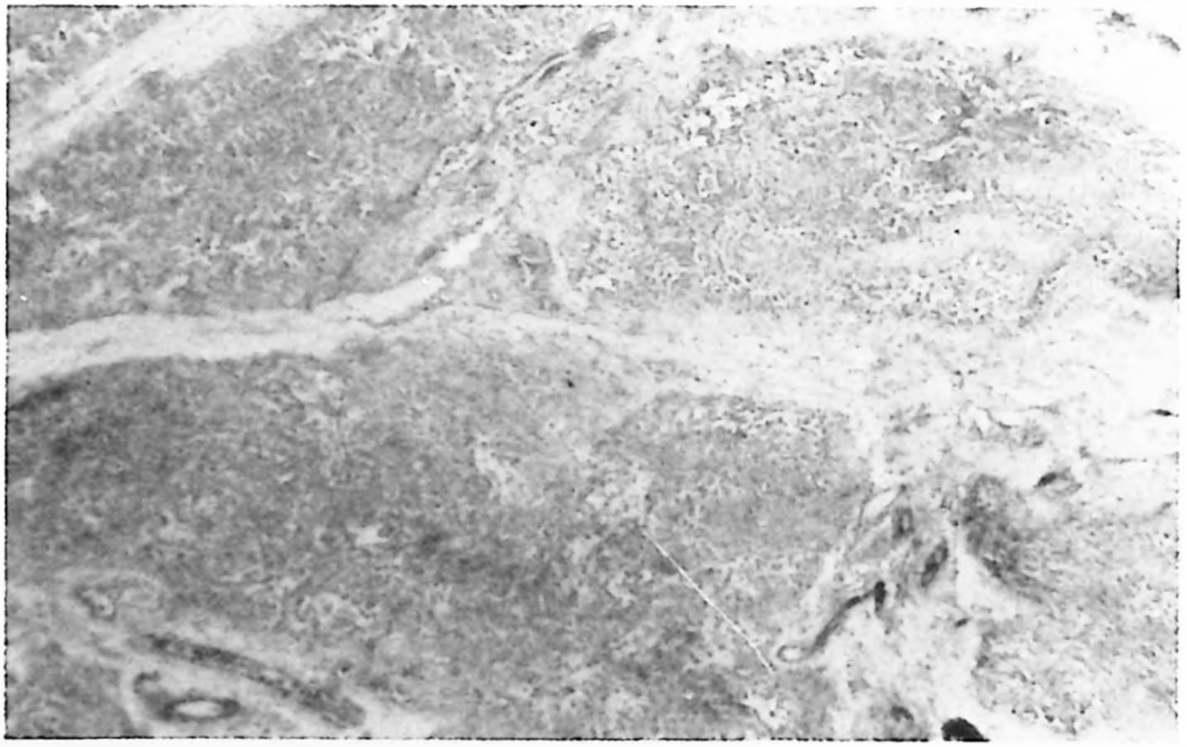

Fig. 2: Thymus showing absence of corticomedullary demarcation and Hassal's corpuscles.

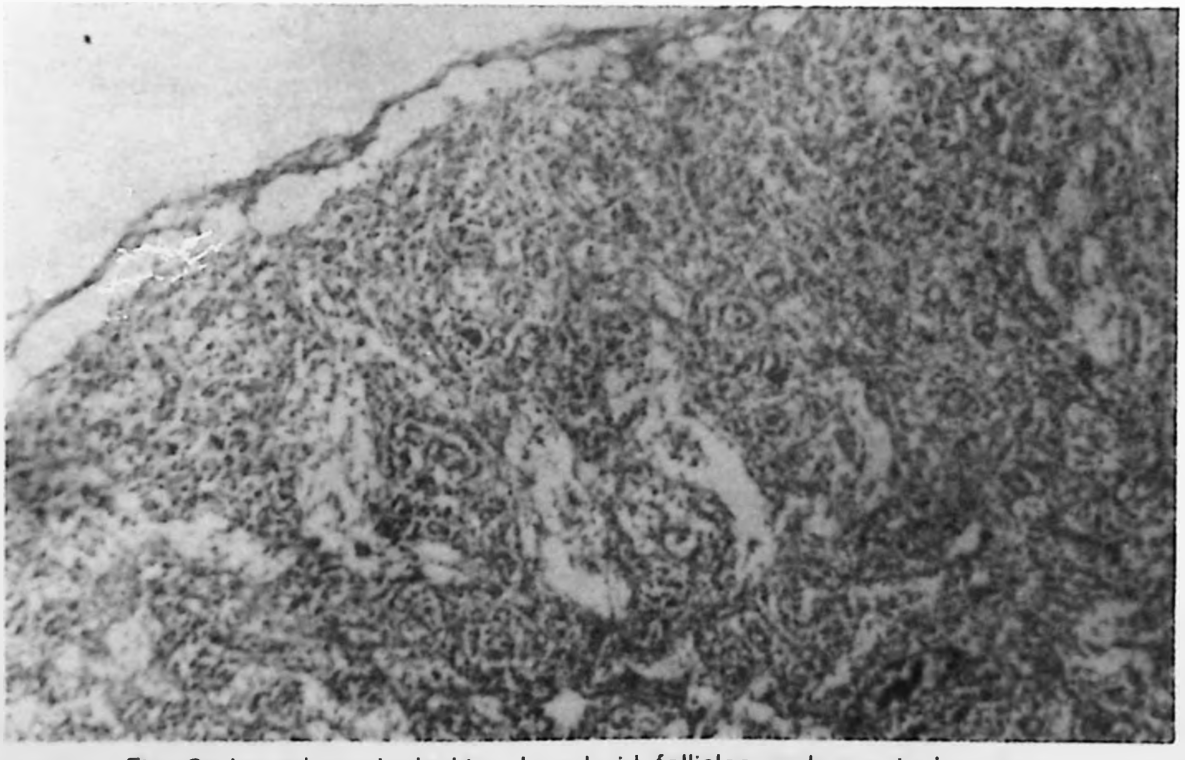

Fig. 3: Lymph node lacking lymphoid follicles and germinal centers.

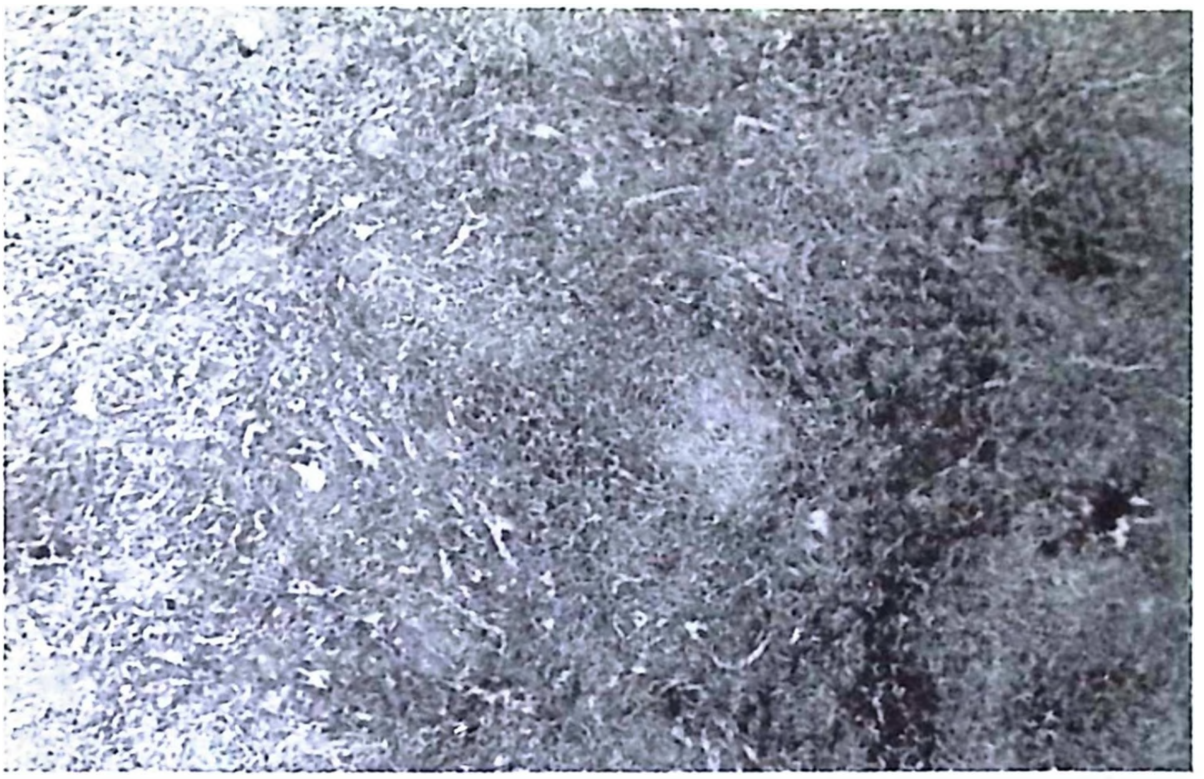

Fig. 4: Lack of lymphoid follicles in white pulp and depletion of lymphocytes in periarteriolar sheats in spleen.

plasma cells were noted in the submucosa (Fig. 5). There were no demonstrable Peyer's patches. The portal areas of the liver were infiltrated by histiocytes, plasmocytoid cells and lymphocytes (Fig. 6).

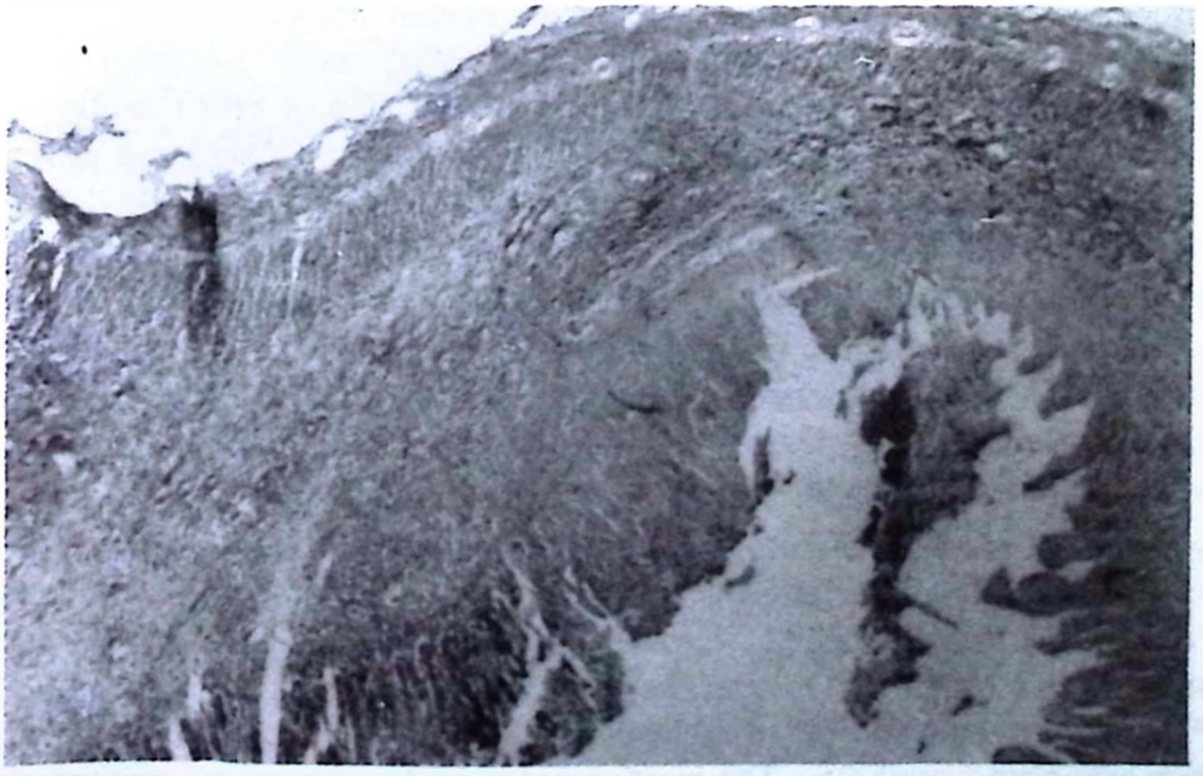

Fig. 5: Ulceration in intestinal tract and scattered plasma cells in submucosa; no demonstrable Peyer's patches.

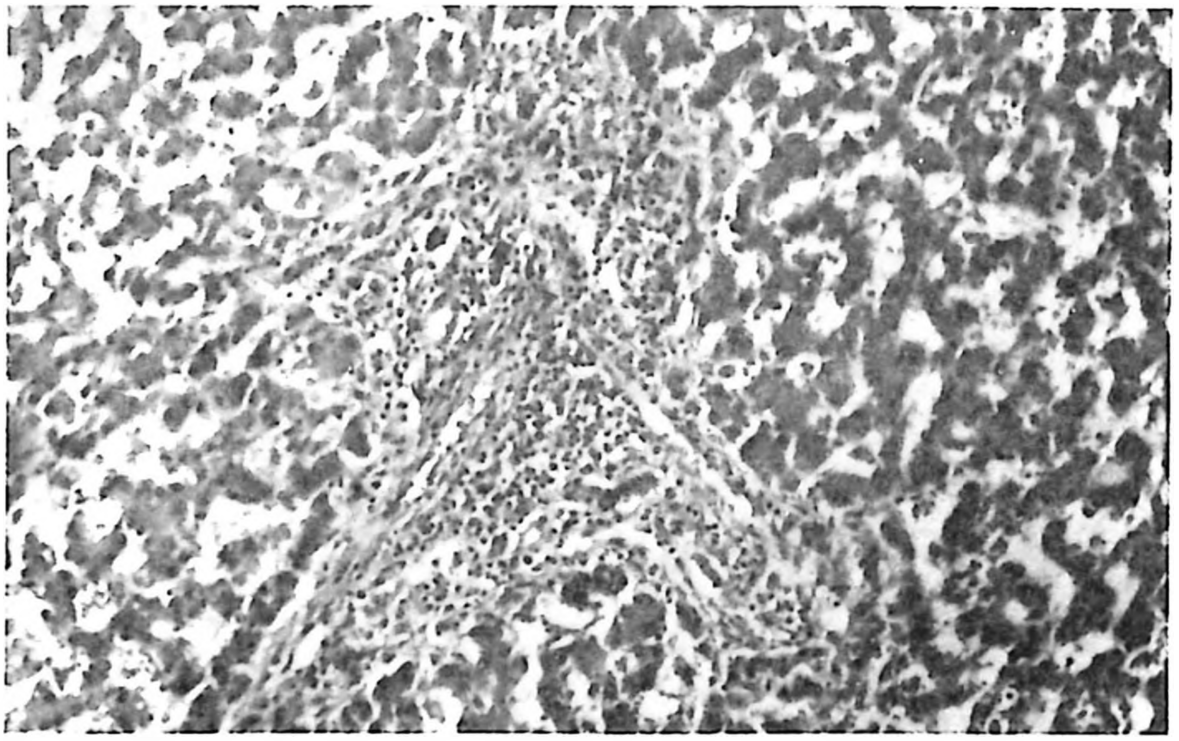

Fig. 6: Infiltration of portal areas by histiocytes, plasmocytoid cells and lymphocytes.

Discussion

We presented two brothers with fatal infectious mononucleosis. The age of onset, clinical course and duration of illness until demise, and the laboratory findings (except serum IgG levels) were similar in these two boys. They demonstrated the diagnostic criteria of XLP[4,2] (e.g., death resulting from a disease whose clinical picture indicated IM, the presence of EBV infection, the failure to mount anti-EBV antibodies, and a mother with both high anti-VCA and anti-EA titers). In addition, the maternal aunts and uncles in this family died of a disease that possibly had an infectious origin or was the result of a birth defect.

In Case 2 morphological alterations of the thymus as well as secondary lymphoid tissues mimicked those seen in patients with severe combined immunodeficiency disease (SCID). Destruction and depletion of the thymus gland have been noted in patients with XLP[2]. Thereafter, these patients develop marked depletion of thymus-dependent regions of the lymph nodes and spleen.

Mroczek et al[6] studied the thymic lesion in 35 XLP syndrome and sporadic fatal IM patients and observed six patterns: 1. Active lymphoproliferation with effacement of Hassal's bodies (HB), 2. Normal appearing HB (only three patients with XLP showed this pattern), however, calcified bodies were seen, precocious for age, 3. Moderate reduction of HB, 4. Marked depletion of HB, 5. Absence of HB, 6. Stress-associated involution. The histopathological findings of our patient were similar to pattern 5.

Possible mechanisms suggested for thymic epithelium destruction in XLP are: 1. Alteration of HLA antigens by viral infection which may lead to misdirected cytotoxic T cells that destroy the epithelium, 2. EBV may cause fusion of lymphoid cells with thymic epithelium leading to entry of virus into the epithelial cells; later epithelial cells undergo necrosis and disappear[2]. In fact, Seshi et al[7] have implanted EBV receptors into thymic epithelial cells by Sendai virus fusion thus creating a portal of entry for the virus. Cells die after several days in culture. It has been suggested that thymic hormones may restore the host immune response in patients with fatal EBV-induced lymphoproliferative disorders (provided that the thymus lesion is a common feature of all individuals)[2].

Recently, restriction fragment length polymorphism (RFLP) markers have been used to localize the XLP locus on the chromosome[8]. With the use of this new technology, it is now possible to predict which members of a family with XLP are carrier females and to diagnose the syndrome prenatally[8].

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