

## Infectious Mononucleosis

### The Spectrum of Morphologic Changes Simulating Lymphoma in Lymph Nodes and Tonsils

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Lymph-node and tonsillar biopsies occasionally are obtained from patients with the infectious mononucleosis syndrome secondary to Epstein-Barr viral infection, particularly if the clinical presentation is atypical and a viral etiology is not suspected. The presence of Reed-Sternberg-like cells in infectious mononucleosis resulting in confusion with Hodgkin's disease is well-known; however, similar difficulty in excluding a non-Hodgkin's lymphoma can be encountered. Eleven cases of reactive lymphoid hyperplasia with the morphologic features of infectious mononucleosis are reported, nine of which had documented Epstein-Barr viral infection. The spectrum of morphologic changes associated with Epstein-Barr viral infection is discussed, with emphasis on the features that permit their distinction from non-Hodgkin's lymphoma. Morphologic features mimicking lymphoma included extensive immunoblastic proliferations in sheets and nodules and marked cytologic atypia. Hodgkin's disease was simulated by the tendency in some cases for the atypical Reed-Sternberg-like cells to cluster about necrotic foci and to show pronounced cytologic atypia. Features permitting the distinction from non-Hodgkin's lymphoma included persistent reactive foci with the classic features of infectious mononucleosis, a polymorphous background of transformed lymphocytes rather than irregular or twisted lymphoid cells as seen in non-Hodgkin's lymphoma, and preservation of underlying reticulin architecture rather than destruction, even in cases with extensive immunoblastic proliferation. Hodgkin's disease was excluded by requiring strict criteria for Reed-Sternberg cells and noting the reactive background as inconsistent with Hodgkin's disease. Immunoperoxidase staining of seven of the cases with anti-Leu-M1 failed to demonstrate immunoreactivity of the Reed-Sternberg-like cells with this monoclonal antibody.

**Key Words:** Infectious mononucleosis—Lymphoma—Atypical lymphoid hyperplasia—Hodgkin's disease.

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The histopathology of infectious mononucleosis (IM) and other morphologically related entities, such as Dilantin hypersensitivity and postvaccinal lymphadenitis, have been reviewed extensively to familiarize pathologists with the morphologic features that will permit their distinction from malignant lymphoma (2,4,8,12,13,28,31,35-37,41). The description of Reed-Sternberg-like cells in IM (28,29,40,41) generated a great deal of interest, since these reports coincided with the publication and acceptance of the Lukes and Butler classification of Hodgkin's disease (24,25), and were a component of ongoing discussions concerning the specificity of the Reed-Sternberg cell (28,29,40). As a result, the literature tends to emphasize the differential diagnosis of IM with Hodgkin's disease, with criteria for distinguishing IM from non-Hodgkin's lymphoma somewhat less precise in comparison. Recently described entities, such as T-zone lymphoma (7), peripheral T-cell lymphoma (44), and T-immunoblastic sarcoma (26), share some features with IM, such as Reed-Sternberg-like cells, proliferation of immunoblasts, paracortical involvement with persistent follicles, prominent postcapillary venules, and a marked inflammatory background. Thus, these lesions must be considered in the differential diagnosis as well, particularly since they have been incorporated to some extent into the working formulation of non-Hodgkin's lymphomas (34). In recent years, several cases of lymph-nodal and tonsillar biopsies from patients with IM have been reviewed in consultation by one of the authors (C.W.B.). The primary problem in differential diagnosis lay in excluding a non-Hodgkin's lymphoma, with Hodgkin's disease a minor consideration in the differential. These cases form the basis of this report. An additional feature of the study involves immunoperoxidase staining of seven cases with anti-Leu-M1, a monoclonal antibody directed

against myelomonocytic cells (11) that has been utilized as a marker for Hodgkin's disease (6,18,20,30).

### MATERIALS AND METHODS

This study is based on 11 cases of reactive or atypical lymphoid hyperplasia, from the consultation files of one of the authors (C.W.B.), in which a diagnosis of IM was documented clinically or suspected morphologically. A clinical diagnosis of IM was confirmed in nine cases on the basis of appropriate clinical symptoms and signs, peripheral blood lymphocytosis with atypical lymphocytes, and a positive monospot or specific Epstein-Barr viral (EBV) serology (5,15-17). The referring pathologists were contacted for additional clinical information, including laboratory data and follow-up; blocks were supplied as available for additional hematoxylin-and-eosin stains, reticulin stains, and immunoperoxidase studies.

Immunohistochemical staining for Leu-M1 was performed on B-5 or formalin-fixed tissue by using a modification of the avidin-biotin-peroxidase complex (ABC) method as described by Hsu and co-workers (19). Briefly, paraffin sections were dewaxed by heating at 60°C, followed by immersion in xylene and a graded series of alcohol. B-5 fixed sections were demercurialized between these steps in a 1% solution of iodine in xylene. Following a brief rinse in distilled water, endogenous peroxidase activity was blocked by incubating the sections in 0.3% H<sub>2</sub>O<sub>2</sub> in methanol for 30 min. Then the sections were incubated sequentially in normal horse serum, a 1:100 dilution of Leu-M1 (Bectin-Dickinson, Mountain View, CA, U.S.A.), biotinylated horse antimouse serum, and ABC (Vector Laboratories, Burlingame, CA, U.S.A.) for 30 min each. Ten-minute rinses in phosphate-buffered saline pH 7.6 were interspersed between steps, except that the sections were blotted only between the normal horse serum and Leu-M1 incubations. Following ABC, the slides were incubated with diaminobenzidine tetrahydrochloride and H<sub>2</sub>O<sub>2</sub> in tris buffer at 37°C for 5 min. The slides then were counterstained in hematoxylin.

For negative controls, the sections were incubated with a 1:100 dilution of purified mouse myeloma protein (Ig6) (Sigma Chemical Company, St. Louis, MO, U.S.A.) instead of Leu-M1. For a positive control, a known case of Hodgkin's disease was included in each run. Polymorphonuclear leukocytes also reacted suitably as an internal positive control.

### RESULTS

The clinical data for the patients included in the study are summarized in Table 1. Although a viral etiology was not established in cases 10 and 11, the florid reactive changes present were identical to those seen in IM and presented the same degree of difficulty in differential diagnosis. These cases are included in order to emphasize that the morphologic criteria presented here are not specific for IM.

In every case, the referring diagnosis was atypical or reactive hyperplasia, and no patient received treatment for a malignant tumor. This statement, however, obscures the diagnostic difficulties encountered. Only case 4 was considered benign outright and was referred with the specific question as to whether the lymph node showed evidence of IM. Six cases were thought to be probably reactive, but with a malignant tumor not completely excluded as a possibility; in four cases, an initial impression of large-cell or immunoblastic lymphoma had been revised in light of a subsequent clinical diagnosis of IM or other viral syndrome. Since the question of Hodgkin's disease was raised specifically in only three cases, the problem in differential diagnosis clearly lay in excluding a non-Hodgkin's lymphoma.

The following case reports are presented to illustrate the varied clinical circumstances in which patients with IM may be subjected to biopsy.

#### Case 5

This 20-year-old man presented with recent onset of fatigue, cough, night sweats, and lymphadenopathy. Physical examination revealed cervical lymphadenopathy and an ulcerated right tonsillar lesion which was biopsied. The 0.6 × 0.4 × 0.2 cm fragment of tissue was interpreted as probable malignant neoplasm, most likely large-cell lymphoma (Fig. 1). A rebiopsy of the tonsillar lesion or lymph-node biopsy was recommended to confirm the diagnosis further. Subsequently, the pathologist was informed that the patient had an atypical peripheral lymphocytosis and a positive monospot test. A cervical lymph-node biopsy specimen showed reactive lymphoid hyperplasia. After several weeks, the patient recovered. The conclusion was made that all clinical and pathologic findings were thought to be secondary to his viral syndrome. A tonsillectomy performed following resolution of his symptoms showed no evidence of the atypical infiltrate.

#### Case 2

This 37-year-old man presented with abdominal pain and fever following a viral upper respiratory

TABLE 1. Clinical data

Case no.	Age	Sex	Clinical presentation	Peripheral blood lymphocytosis	Serology	Extent of adenopathy	Site of biopsy	Length of follow-up period
1	50	F	Pharyngitis and constitutional symptoms	Moderate atypical lymphocytosis	Positive monospot, specific titers for EBV	Tonsils, bilateral, massive	Tonsil	2 yr
2	37	M	Upper respiratory infection, abdominal pain, hepatic dysfunction	8,064 (absolute) 36% atypical	Positive specific titers for EBV and cytomegalovirus	Retroperitoneal	Retro-peritoneal	2 mo
3	38	M	Cold-like symptoms, fatigue	46% lymphocytes 11% atypical	Positive monospot	Cervical x 6 mo	Cervical	4 mo
4	13	F	Asymptomatic	80% lymphocytes (5,400 absolute)	Positive monospot	Cervical	Cervical	3 yr
5	20	M	Sore throat, cough, night sweats, fatigue	"Atypical lymphocytosis"	Positive monospot	Cervical, ulcerated right tonsil	Tonsil, cervical	6 wk
6	15	M	Sore throat	21% atypical lymphocytes	Positive monospot	Tonsils	Tonsillectomy	10 mo
7	14	F	Dysphagia	48% lymphocytes	Positive monospot	Tonsils, cervical	Cervical	None
8	18	M	Sore throat, splenomegaly	6,700 lymphocytes (absolute), many atypical	Positive monospot	Cervical, axillary, exudative tonsillitis	Cervical	9 mo
9	29	M	Malaise, fever, weight loss	"Atypical lymphocytosis"	Positive monospot	Cervical, submandibular, supraclavicular	Supra-clavicular	1 mo
10	14	M	Asymptomatic	None	Negative monospot	Axillary, inguinal	Axillary	3 yr
11	26	F	Asymptomatic	None	Negative monospot	Cervical	Cervical	5 yr

infection. Abnormal liver functions were noted on admission; subsequently, the patient developed pleural effusions and ascites.

The initial white blood cell count, monospot, and EBV and cytomegaloviral titers were not elevated.

Abdominal sonography and computed tomography (CT) scan revealed hepatosplenomegaly, a thick-walled gallbladder with stones, and retroperitoneal adenopathy. A cholecystectomy with liver and lymph-node biopsies was performed. The lymph-

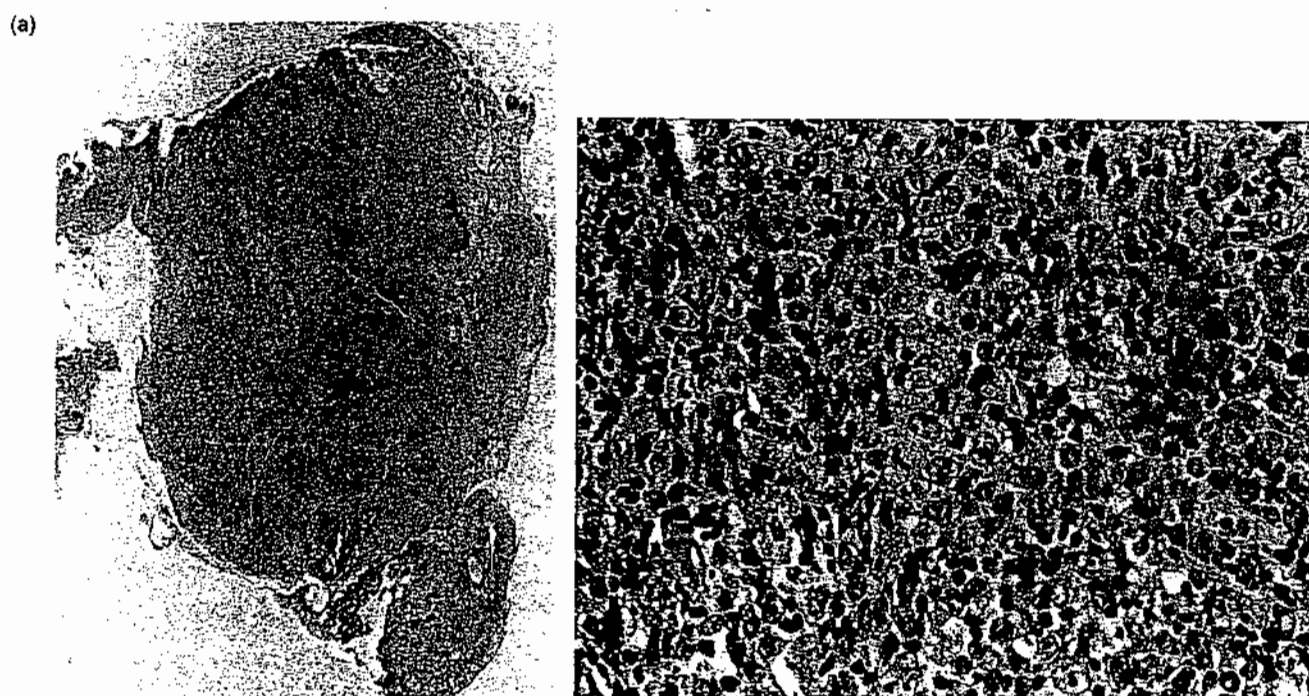


FIG. 1. Case 5, tonsil. (a) The tonsillar architecture is inapparent in the face of a diffuse infiltrate. (b) At high power, numerous immunoblasts are admixed with a minor population of small, mature lymphocytes.

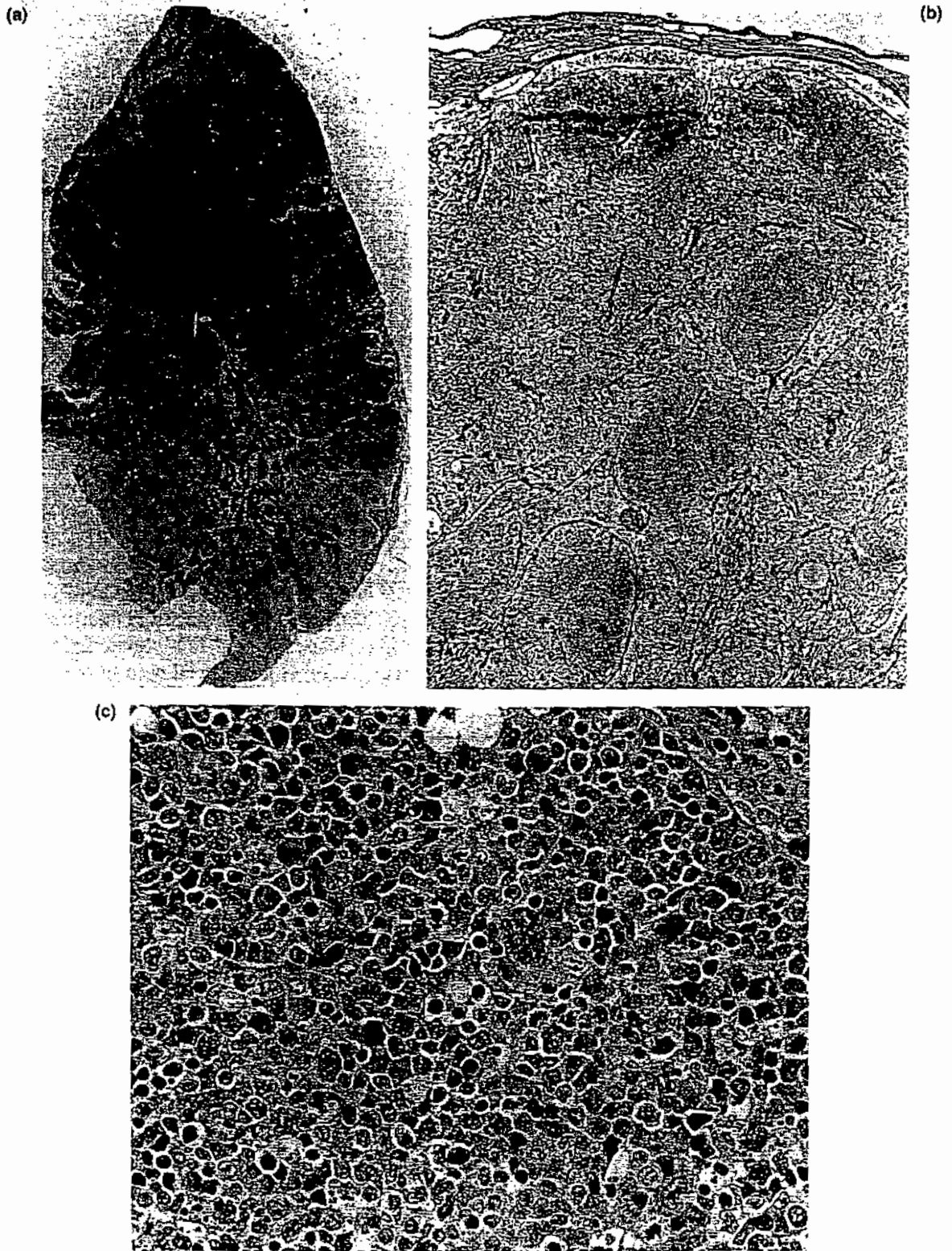


FIG. 2. Case 2, lymph node. (a) Whole mount showing intact architecture. (b) Note foci of mature lymphocytes in cortical and medullary regions with the reticulin structure of follicles. (c) Polymorphous hyperplasia. Note the bizarre nuclear features of the large cell in the center.



node and liver biopsy specimens were interpreted initially as showing malignant lymphoma, large-cell, immunoblastic type (Figs. 2 and 3). On the day of surgery, an atypical lymphocytosis first appeared. Postoperatively, the patient developed respiratory distress, continued to gain weight, and had increased pleural effusions, ascites, and peripheral edema. However, by discharge on the eighth postoperative day, his condition had improved markedly with resolution of his clinical signs and symptoms. Prior to discharge, it was decided that the hepatic dysfunction and lymphadenopathy were secondary to a viral syndrome. When seen 1 month later, he was essentially asymptomatic, with hepatosplenomegaly and adenopathy resolved on CT scan. Convalescent cytomegaloviral and EBV titers showed diagnostic elevations. Review of the liver biopsy specimen showed lymphoid infiltrates within enlarged portal tracts. Cytomegaloviral inclusions were not seen.

#### HISTOPATHOLOGY

The pathologic findings are summarized in Table 2. The histopathology of IM in lymph nodes has been described in detail in several excellent reviews (4,8,31,36,41) and will be summarized briefly. The commonly recognized features include reactive follicular hyperplasia, paracortical (T-zone) expansion with distortion rather than effacement of the architecture, and at least focal preservation of the sinuses. The sinuses themselves

TABLE 2. Histopathologic features<sup>a</sup>

Histopathologic feature	Case									
	1	2	3	4	5	6	7	8	9	10
Follicles	2+	1+	2+	2+	NE <sup>b</sup>	2+	2+	2+	1+	1+
Paracortical expansion	2+	3+	2+	2+	3+	2+	2+	2+	3+	3+
Immunoblasts	2+	2+	2+	1+	3+	2+	1+	3+	3+	3+
Cytologic atypia	3+	3+	1+	0	1+	2+	1+	1+	1+	1+
Sinus changes	0	3+	1+	2+	0	0	0	3+	1+	1+
Postcapillary venules	2+	3+	2+	2+	1+	2+	2+	2+	3+	3+
Necrosis	1+	0	2+	0	0	3+	0	0	0	0

<sup>a</sup> The features are scored 0 to 3+, depending upon the relative degree of prominence: 0, absent; 1+, mild or rare; 2+, moderate; 3+, extensive, numerous.

<sup>b</sup> Not evaluable. Follow-up biopsy revealed reactive follicles.

frequently are dilated and filled with reactive lymphocytes (Downey cells), immunoblasts, and proteinaceous fluid (Fig. 3). The expanded paracortical zones are characterized by a polymorphous hyperplasia with variable numbers of small and medium-sized (transformed) lymphocytes, immunoblasts, occasional Reed-Sternberg-like cells, and plasma cells in various stages of maturation (Fig. 2c) (23). Recognition of this constellation of morphologic features is a crucial step in the evaluation of the morphology. The cases in our series presented a continuum of morphologic changes recognizable as variations of the above general scheme, varying from the obviously benign to florid changes highly suggestive of malignancy. The general morphologic features cited above were present at least

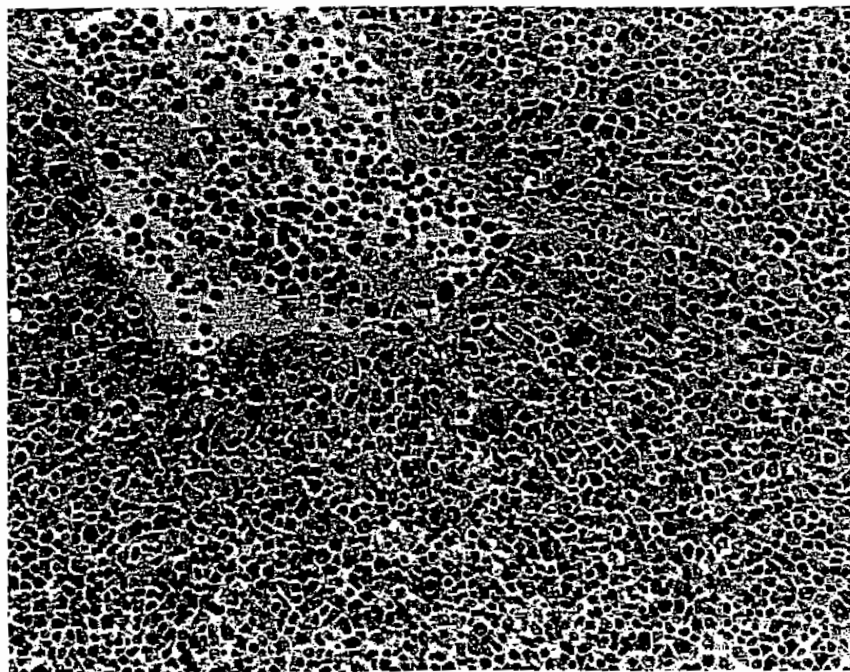


FIG. 3. Case 2, lymph node. The dilated sinus contains the same maturation sequence of transformed lymphocytes as is seen in the adjacent medullary region.

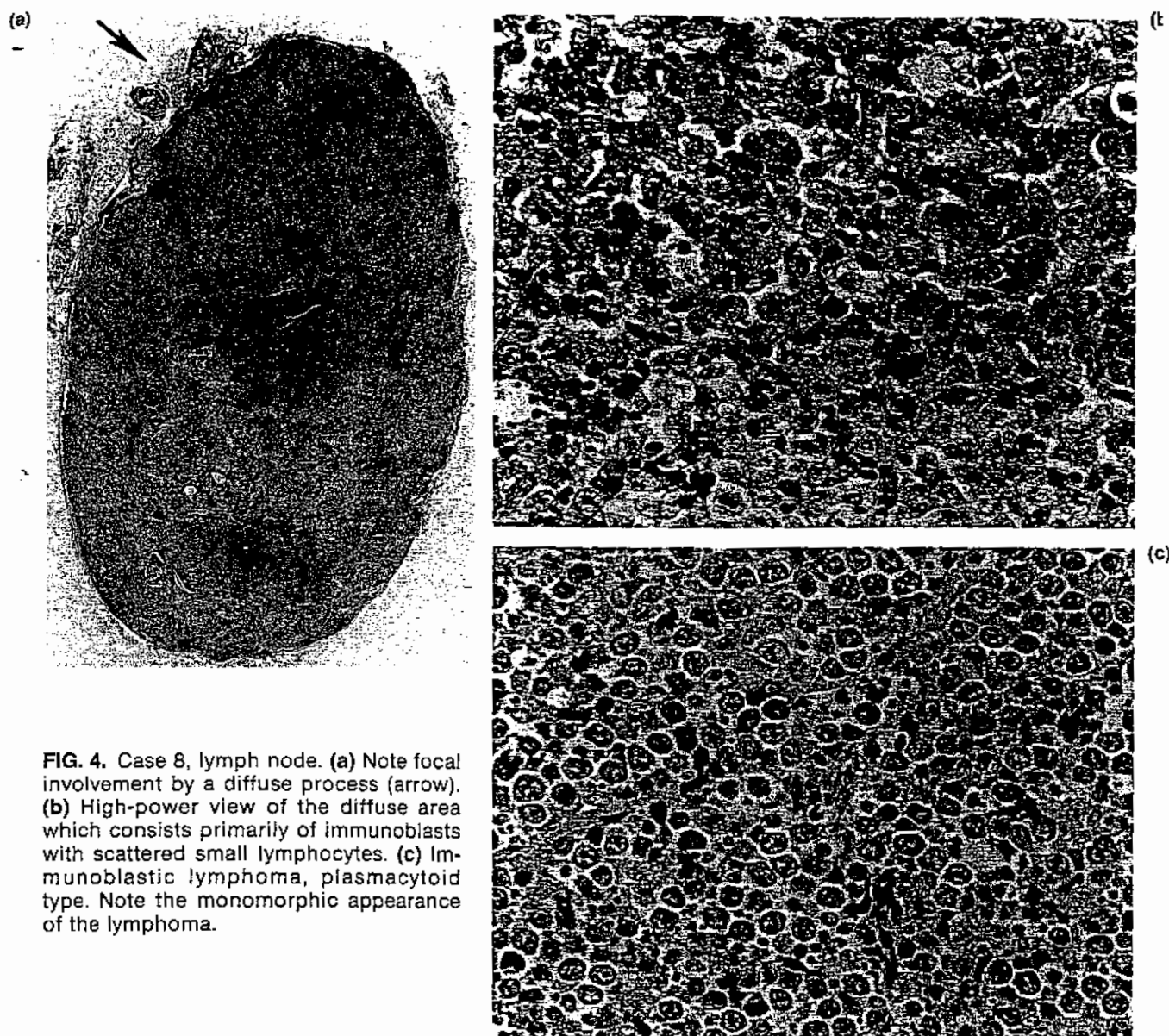


FIG. 4. Case 8, lymph node. (a) Note focal involvement by a diffuse process (arrow). (b) High-power view of the diffuse area which consists primarily of immunoblasts with scattered small lymphocytes. (c) Immunoblastic lymphoma, plasmacytoid type. Note the monomorphic appearance of the lymphoma.

focally in every case, but varied in their relative contribution to the overall histology. Six cases (nos. 1, 3, 4, 6, 7, and 8) were characterized by prominent follicular and paracortical hyperplasia, as described for the "mixed" pattern of reactive lymphoid hyperplasia by Dorfman et al. (4) (Fig. 4). Five cases (nos. 2, 5, 9, 10, and 11) showed a marked paracortical expansion at the expense of the follicles, which were demonstrable in two cases only with reticulin stains (Fig. 2); these stains revealed the characteristic preservation of architecture despite an appearance of being partially overrun by immunoblasts. In general, the polymorphous nature of the paracortical hyperplasia was apparent. However, cases 5, 8, 9, and 10 were disturbing in that the immunoblasts tended to be ex-

ceedingly numerous in large aggregates or sheets, such that the lymphoid "maturation" sequence characteristic of polymorphous hyperplasia was less apparent (Fig. 4). The expanding "nodules" of immunoblasts typically merged imperceptively with the adjacent paracortical zones and follicles, so that a clear demarcation between "involved" and "uninvolved" node was not present (Fig. 4).

The cytologic atypia seen in IM has been well documented (2,4,8,13,28,29,31,36,37,40,41). In our experience, the degree of atypia varied from case to case and was marked in only three of the cases. Although rare binucleated immunoblasts were present in every case, if carefully sought, distinction from Reed-Sternberg cells was generally straightforward. The nucleoli were small, single to multiple,

irregular in shape, and lacked the inclusion-type of appearance characteristic of Hodgkin's disease. In the three cases in which cytologic atypia was a significant factor, lobulated Reed-Sternberg-like cells were numerous, exhibited marked nuclear pleomorphism, and had unusual eosinophilic inclusion-like nucleoli (Fig. 5). Atypical cells tended to cluster near the necrotic tonsillar crypt epithelium or singly in the paracortex, medullary cords, or peripheral sinuses. The polymorphous background was difficult to discern in some high-power fields (Fig. 5).

Frank necrosis was present in three cases, although the "mottled" appearance of the paracortex frequently was due to numerous tingible body macrophages. Case 3 showed the classic reactive changes of IM, with approximately 10% of the cut surface showing confluent necrosis (Fig. 6).

#### IMMUNOPATHOLOGY

Cases 1, 2, 3, 4, 5, 10, and 11 were stained with anti-Leu-M1. The only positive cells were neutrophils and occasional histiocytes which served as in-

ternal positive controls and were seen in every case. The immunoblasts and Reed-Sternberg-like cells were uniformly negative.

#### DISCUSSION

The IM syndrome associated with EBV infection can be considered a benign self-limited lymphoproliferative disorder (3), although fatal cases have been described (27,32,33,39). Fatal IM is one phenotypic expression of the X-linked lymphoproliferative syndrome (32,33). In addition to IM, EBV infection has been associated with Burkitt's lymphoma and nasopharyngeal carcinoma (14,15).

Lymph-nodal biopsies rarely are performed when patients present with the classic seropositive IM syndrome, partly out of fear of an erroneous diagnosis of malignancy. Lymphoma can be a clinical consideration in patients with an atypical presentation in which a viral etiology is inapparent. The limitations of peripheral blood changes and heterophile antibody testing for the diagnosis of IM are well-known (5,15,16); occasional patients require repeated testing or EBV specific antibody de-

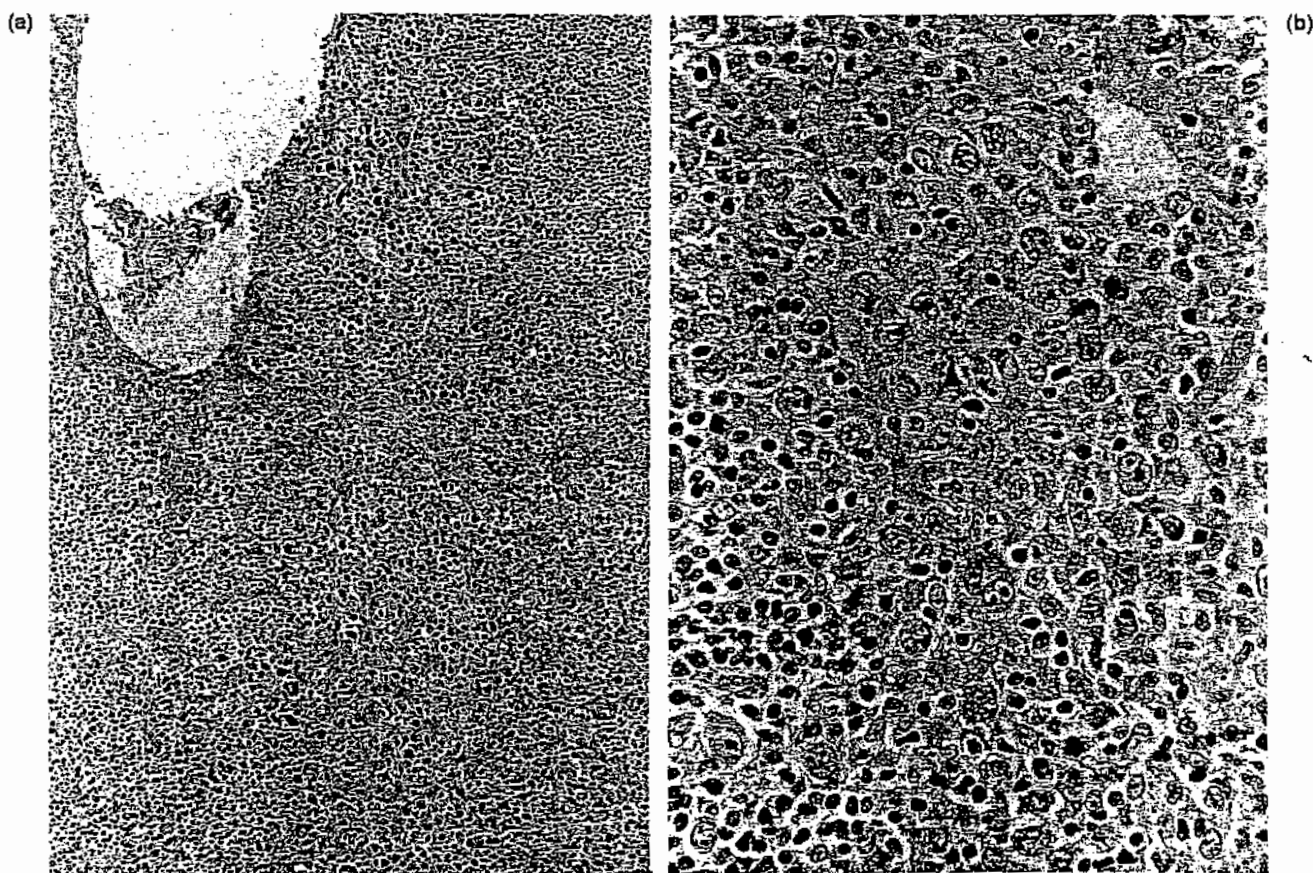


FIG. 5. Case 1, tonsil. (a) Mixed infiltrate adjacent to the crypt epithelium. (b) High-power of (a) showing numerous Reed-Sternberg-like cells with eosinophilic inclusion-like nucleoli.



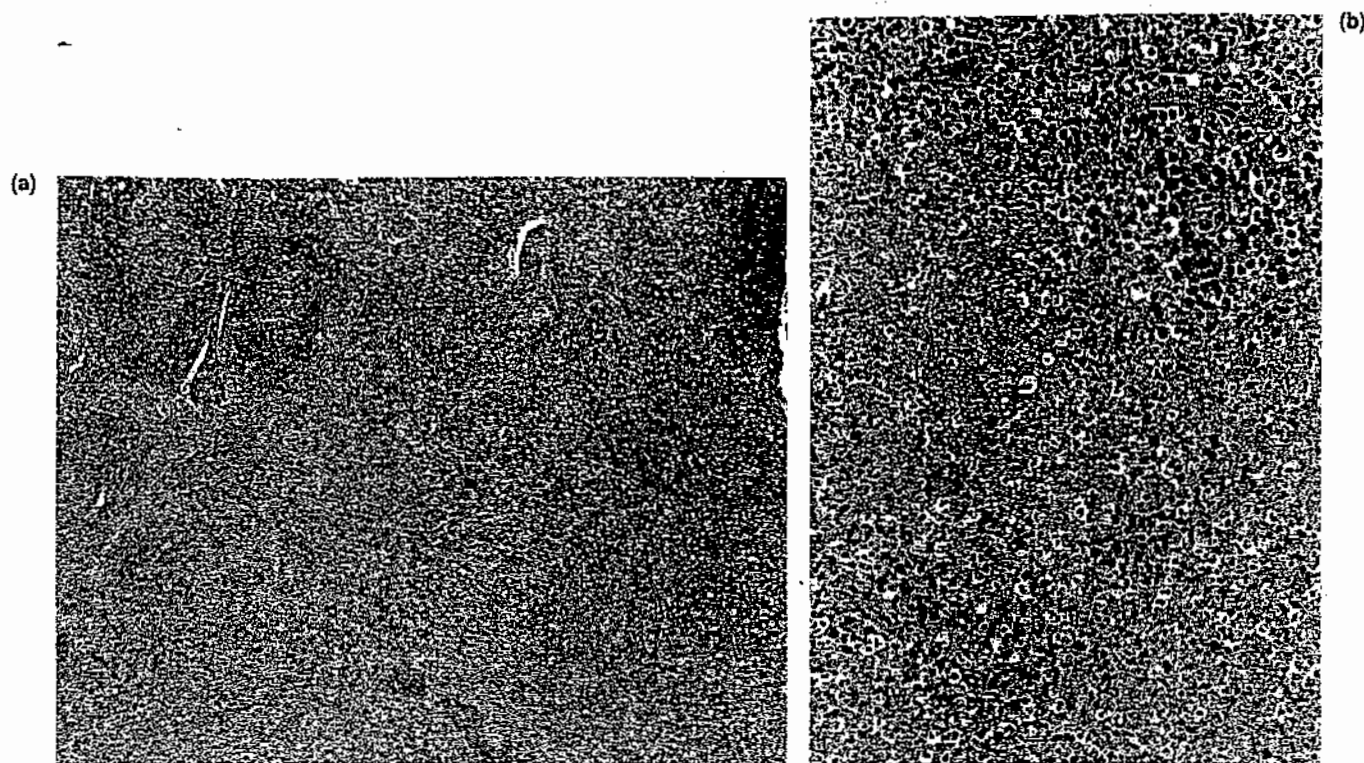


FIG. 6. Case 3, lymph node. (a) Expanded paracortex with a mottled appearance. Note reactive germinal centers with well-developed mantles. (b) Foci of necrosis were present. Note viable cells clustered around capillaries, simulating tumor necrosis.

terminations (15). A chronic form of EBV infection is now recognized that is not always associated with persistent heterophile antibodies (10,42). The patients experience fevers, lymphadenopathy, and weight loss over a period of months to several years (10,42), and easily can be suspected of harboring lymphoma. Patients may have viral syndromes other than EBV, which may be missed if the serologic examination is confined to a monospot test. Clearly then, situations can occur in which the clinical documentation of EBV or other infection is lacking at the time of pathologic examination and therefore, cannot prejudice the pathologist in favor of a benign diagnosis. Conversely, lymphoma is not excluded simply by showing serologic evidence of EBV infection. Hodgkin's disease and Burkitt's lymphoma have been reported in seropositive individuals (1,9,43) and false positive monospot tests can occur in patients with lymphoma (45).

The diagnosis of reactive lymphoid hyperplasia in the setting of EBV infection is straightforward when reactive follicles, sinus changes, and mild paracortical expansion with scattered immunoblasts are present throughout the node. When extensive, the immunoblastic proliferation occurring in nodules and sheets can dominate the histologic appearance, partially obscuring the other reactive

features and suggesting partial involvement by large-cell lymphoma, immunoblastic type. Figure 4 demonstrates the similarity between the reactive immunoblastic proliferation and immunoblastic lymphoma. In other cases, marked cytologic atypia may suggest lymphoma. There are, however, several characteristic features of IM (summarized in Table 3) which are important to recognize as indicative of reactive hyperplasia. Each feature does not necessarily constitute an independent diagnostic criterion. For example, it is not unusual to find atypical cells in the sinuses of lymph nodes involved by lymphoma or an occasional residual follicle. In the aggregate, however, these findings justify a benign diagnosis. The crucial step in evaluating these cases is the recognition of the classic changes of IM (reactive follicles, "mottled" paracortex, and sinus changes) elsewhere in the nodes at least focally (or in another biopsy, as in case 5). The nodules and sheets were never completely monomorphic, showing a definite, albeit minor, population of mature and transformed lymphoid cells as seen in polymorphous hyperplasia. The nodules were not sharply demarcated, and tended to merge imperceptibly with the reactive follicles and paracortical zones (8,41). The underlying architecture remains intact, with the reticulin struc-



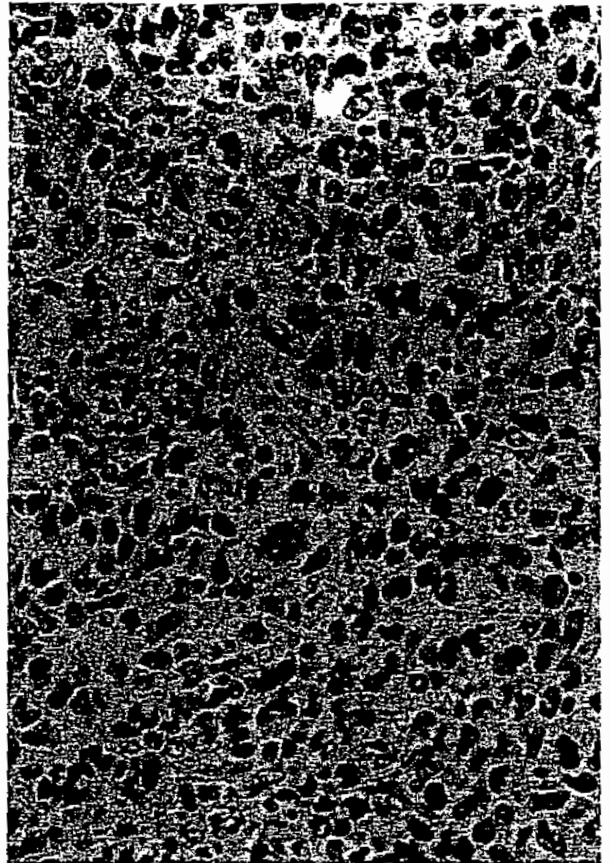
**TABLE 3. Morphologic findings in IM, the combined presence of which allows the distinction from non-Hodgkin's lymphoma**

Presence of the classic features of IM, at least focally:
Reactive follicles
"Mottled" paracortical expansion
Sinus changes (see text)
Polymorphous background composed of reactive or transformed lymphocytes
Preservation of reticulin architecture rather than effacement
Merging of immunoblastic proliferation with reactive follicles and paracortex.

ture preserved. The reticulin stain occasionally reveals obscured reactive follicles, even when apparently overrun by proliferating immunoblasts. Complete effacement of the lymph-nodal architecture in IM has not been described (4,8,31,36,41) and was not seen in our cases.

Cytologically, the Reed-Sternberg-like cells can be indistinguishable from those seen in malignant lymphoma, mixed small- and large-cell or immunoblastic, polymorphous type (34). In the reactive condition, the background cells show a maturation sequence of transformed lymphocytes and plasma cells, as contrasted with the twisted, folded, and angulated nuclear configuration of the non-Hodgkin's lymphoma (Fig. 7). The differential diagnosis of IM and Hodgkin's disease has been discussed thoroughly (4,8,36,41). In summary, the distinction between IM and Hodgkin's disease is accomplished by recognizing the lymphoid background in IM as reactive and, therefore, inconsistent with a diagnosis of Hodgkin's disease, and by requiring strict criteria for the identification of the Reed-Sternberg cells (4,24,28). In rare cases, the Reed-Sternberg-like cells in IM can be indistinguishable from Hodgkin's disease. In this circumstance, the diagnosis will be dependent upon recognition of the reactive background in IM as compared to the innocuous, unstimulated appearance of the lymphoid cells in Hodgkin's disease. Frequently (but not always) the immunoblasts in IM are far too numerous in proportion to the binucleated forms or Reed-Sternberg-like cells to be consistent with Hodgkin's disease. The architectural localization of the atypical cells in IM is important. In the tonsils or lymph nodes, the Reed-Sternberg-like cells can cluster around necrotic crypts or foci, closely simulating Hodgkin's disease. If only an incisional biopsy is performed, the distinction from lymphoma may be impossible and additional specimens must be taken.

Anti-Leu-M1 is a monoclonal antibody primarily directed against myelomonocytic cells, although it will react with some T-cell lines and mitogen acti-



**FIG. 7.** Diffuse small- and large-cell lymphoma. Note markedly irregular, angulated, and convoluted nuclear features of the smaller lymphoid cells.

vated T cells (11). The antibody stains Reed-Sternberg cells and their variants in the majority of the cases tested, and is gaining popularity as a marker for Hodgkin's disease (6,18,20,30), despite reports of positive staining in non-Hodgkin's lymphomas of T-cell origin (21,22,38). Positive staining of lymphoid cells generally is not seen in reactive conditions to any extent (30), although occasional Leu-M1 positive Reed-Sternberg-like cells were described in a biopsy specimen interpreted as angioimmunoblastic lymphadenopathy (21). A single case of IM has been reported as negative (21). In our series, the only positive cells were neutrophils and occasional benign macrophages; the immunoblasts and Reed-Sternberg-like cells were uniformly negative. These findings suggest that anti-Leu-M1 positive atypical cells, when numerous, may be more consistent with a malignant neoplasm, the exact nature of which would remain to be established on the basis of morphologic criteria.

The diagnostic problems presented by EBV infections continue to be a concern for the practicing pathologist. The reactive nature of these lesions can be recognized on the basis of characteristic

morphologic features. An erroneous diagnosis of lymphoma can be avoided by applying strict criteria for the diagnosis and by maintaining an awareness of the clinical setting in which lymph-nodal biopsies are performed. □

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