Fine Needle Aspiration Biopsy Diagnosis of Histiocytosis-X: A Brief Review

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The term histiocytosis-X (Hx) was suggested by Lichtenstein in 1953 as a broad general designation for a disease complex consisting of three clinical syndromes; namely, eosinophilic granuloma, Hand-Schuller-Christian disease, and Letterer-Siwe disease. Lichtenstein favored abandoning the use of eponyms because several cases could not be categorized precisely due to overlapping clinical and microscopic features. Histiocytosis has the connotation of an inflammatory proliferative reaction of histiocytes, and histiocytosis-X denotes unknown nature of the condition [1]. Several detailed studies regarding the pathology and pathobiology of Hx have been published [2-5]. Experience with a series of Saudi patients was reported earlier from our laboratory [6].

The etiology and pathogenesis of Hx remain unclear. Although it is generally agreed that in Hx there is proliferation of cells identical to or closely related to Langerhans histiocytes (LC), which belong to the mononuclear phagocyte and immunoregulator (MPire) system [7], the manner in which this proliferation is brought about is subject to considerable speculation. There are three broad hypotheses regarding the mechanism and nature of LC proliferation [7]. First, proliferation of LC may be a normal response to an unknown exogenous agent, most likely an infectious pathogen such as a virus or bacteria. However, no such organism has ever been demonstrated. Second, the LC proliferation may be a neoplastic process. Acute fulminant disease as seen in Letterer-Siwe disease may provide support for such a concept although localized lesions are obviously non-neoplastic. The third hypothesis implies that LC are responding to an abnormal signal from another component of the immune system, such as T-cells. It may also be suggested that perhaps Hx is not a single disease with single pathogenesis. In view of the wide spectrum of clinical manifestations, it may be speculated that a variety of etiologic factors rather than a single cause are involved in the pathogenesis of this lesion.

The first step in the management of this disease is to be certain of the diagnosis. Although the diagnosis may be suggested in many cases by consistent clinical findings, it can only be confirmed by appropriate pathology. Therefore, the biopsy of the suspected lesion is the only definitive test. The conventional method for diagnosing Hx is to obtain a surgical biopsy which is examined histologically. However, in recent years several studies have demonstrated the feasibility of diagnosing Hx by fine needle aspiration biopsy (FNAB) [8-13]. The purpose of this communication is to briefly review the various aspects of FNAB diagnosis of Hx in light of experience in our laboratory as well as studies published from other institutions. We hope this will be of help to those interested in the diagnosis and management of this interesting and intriguing disease.

Histiocytosis-X is histologically characterized by proliferation of large numbers of Langerhans cells which are characterized by markedly indented "coffee bean" nuclei and moderate amount of light staining cytoplasm [3,4]. These histiocytes usually lack phagocytosis and are mixed with a variety of other cells including eosinophils, neutrophils, plasma cells, and macrophages. Some of the macrophages may have foamy cytoplasm. Variable numbers of multinucleated giant cells are usually present (Figure 1). Areas of necrosis and fibrosis may also be present. The lesions may be solitary or multicentric and may affect almost any organ in the body, although there is a predilection for certain organs such as bones, skin, and reticuloendothelial system [2-5].
The morphologic features of Hx in the FNAB smears are essentially similar to those in the histologic sections.
Consequently, FNAB diagnosis of Hx is also dependent upon the recognition of large numbers of LC in addition to other cell types [8-13]. LC is seen in aspiration smears as polygonal loosely arranged cells with a moderate amount of cytoplasm and irregular cell outlines. Most of the cells have ovoid nuclei with prominent indentations and grooves (Figure 3). These cells, although histiocytic in nature, lack any significant phagocytosis [3]. The relative proportion of other cell types present within these lesions varies considerably from one case to the other and occasionally from one area of the lesion to the other. When these cells are present in large numbers, they tend to mask the LC, thus making their recognition difficult. In such cases, additional, more specialized, techniques such as electron microscopy and immunocytochemistry may be required for arriving at a precise and definitive diagnosis.

Electron microscopy of the FNAB sample may be extremely useful in establishing a precise diagnosis in a variety of neoplastic and nonneoplastic conditions [14-16]. The material derived from FNAB may be easily processed for electron microscopy using simple techniques [17]. On electron microscopy, the LC have round to irregular cell outlines with several small cell processes extending out from the periphery. The cytoplasm is usually rich in organelles containing well developed Golgi complexes, profile of rough and smooth endoplasmic reticulum, lysosomes and deposits of glycogen (Figures 4 and 5). On higher magnification, some of the lysosomes may have a lamellar pattern. The most characteristic ultra-structural feature of LC, however, is the presence of Birbeck granules. These are elongated pentalaminar bodies with central cross-striation (Figure 6). These granules are randomly distributed within the cytoplasm, although some are contiguous with the plasma membrane [6,18,19].

FNAB sample may also be processed for a variety of immunohistochemical studies using cytospin preparations [20]. Immunocytochemistry may also help to confirm the diagnosis of Hx by precise identification of LC. Several studies have helped to delineate the immunohistochemical staining patterns of LC [21-23]. Thus, LC are generally negative for leukocyte common antigen, nonspecific esterase, Leu M1, epithelial membrane antigen (EMA) and LN1. On the other hand, most of the cells are usually positive for OKT6, S-100, HLA-DR, C3, Fc receptors, ATPase and peanut agglutinins. Of these, the most widely used marker for LC are S-100 and OKT6. S-100 has the advantage over OKT6 because it can be used for formalin fixed and paraffin embedded tissues whereas OKT6 staining requires frozen tissue sections. Furthermore, S-100 can be reliably used for staining cytospin preparations (Figure 7). None of the above mentioned stains give positive results in 100% of the cases. Therefore, it is advantageous to have a panel of antibodies rather than a single antibody. Because of the presence of a variety of cell types, the histologic as well as cytologic patterns in Hx may vary considerably. In a review of 14 cases from our laboratory, three morphologic patterns were recognized based on the predominant cell type in the aspiration smears [13]. These were: LC predominant pattern, eosinophil predominant pattern, and macrophage predominant pattern (Figures 8-10). These cellular patterns may be a reflection of the duration and chronicity of the lesion. It has been shown that in the early stages, the lesions of Hx are rich in LC and/or eosinophils. Later, there is an increase in the number of macrophages, many of which have abundant foamy cytoplasm. With the passage of time, all these cells gradually decrease in number and the lesion area is replaced by granulation tissue and fibrosis [24]. At this stage, the LC are relatively scanty and may be difficult to demonstrate. Limited surgical biopsies or FNAB samples from these lesions may be difficult to interpret adequately.
The usual morphological appearance of LC is that of roughly polygonal cells with somewhat irregular outlines [8-13]. However, in some cases, these cells may have markedly irregular cell borders with well developed dendritic processes (Figure 11). Such an appearance of LC is uncommon in Hx. In our series of 14 cases, three FNAB revealed at least some LC with well formed dendritic processes [13]. Langerhans cells with prominent dendritic processes have not been documented in any of the other published studies dealing with FNAB diagnosis of Hx; however, the presence of dendritic processes is a characteristic morphologic feature of normal LC in the epidermis [5]. It is not clear why such a feature is not seen more frequently in cases of Hx. The differential diagnosis of Hx is quite variable and may depend to a great extent on the location of the lesion. In cases of skin lesions, the differential diagnosis includes such conditions as juvenile xanthogranuloma, reticulohistiocytoma, urticaria pigmentosa, graft versus host disease, and Kimura disease. Several other inflammatory and neoplastic conditions may show reactive proliferation of LC but are fundamentally different from Hx. These include atopic dermatitis, contact allergic dermatitis, lichen planus, tuberculoid leprosy and mycosis fungoides [25-27]. In the bone lesions, a variety of possibilities such as osteomyelitis, malignant histiocytosis, and monocytic leukemia may have to be considered [5]. In case of lymph nodes, several benign and malignant conditions may superficially mimic Hx [28]. These include granulomatous diseases such as sarcoidosis and tuberculosis, reactive processes such as dermatopathic lymphadenopathy and sinus histiocytosis with massive lymphadenopathy [5]. Some of the malignant processes involving lymph nodes may also be confused with Hx. These include Hodgkin disease, malignant histiocytosis, large cell anaplastic (K-1 positive) lymphoma, and myelomonocytic leukemia. Rarely, localized proliferation of LC and eosinophils may be seen in lymph nodes involved by a malignant neoplasm such as malignant lymphoma, Hodgkin disease and metastatic carcinoma [29-31].
Figure 6. Part of an LC showing Birbeck granules parallel double membranes with characteristic cross striation. A few lysosomes are also present. Uranyl acetate and lead citrate 45000X.

Figure 7. A cytospin preparation from FNAB showing LC stained positively for S-100. Diff-Quik stain 200x.

Figure 8. Aspiration smear showing LC predominant pattern of Hx. Diff-Quik stain 200x.
Figure 9. Aspiration smear featuring eosinophil predominant pattern of Hx. There are numerous eosinophils with a few LC. Diff-Quik stain 200x.

Figure 10. Macrophage predominant pattern of Hx in an aspiration smear. Most of the cells are histiocytes with foamy cytoplasm. Only occasional LC are identified. Diff-Quik stain 200x.

Figure 11. Aspiration smear from Hx featuring several LC with prominent dendritic processes. Diff-Quik stain 200x.
In view of the wide variety of lesions that may have to be considered in the differential diagnosis of Hx, it is crucial to examine and interpret the cytologic smears in full knowledge of the clinical setting. In those cases where the clinical presentation is atypical or the morphologic pattern of the lesion is unusual, histologic confirmation is recommended.

References

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