VULVÁRNA HISTIOCYTÓZA Z LANGERHANSOVÝCH BUNIEK

VULVAR LANGERHANS CELL HISTIOCYTOSIS

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Súhrn: Histiocytóza z Langerhansových buniek je vzácne proliferatívne ochorenie, ktoré má nejasnú etiológiu, pestré klinické symptómy a veľmi široké biologické správanie. Liečba nie je presne definovaná a je veľmi individuálna. Obťažnosť terapie spočíva aj v nemožnosti predpovedať klinický priebeh ochorenia. Sú potrebné ďalšie klinické štúdie s cieľom predikcie priebehu ochorenia a definovania prognostických faktorov. Výskumné úsilie sa musí zamerať na objasnenie patogenézy a vypracovanie racionálnej terapie. Autori článku podávajú prehľad o vulvárnej lokalizácii histiocytózy z Langerhansových buniek a prezentujú súčasnú koncepciu biologických funkcií Langerhansových buniek.

Kľúčové slová: histiocytóza z Langerhansových buniek, vulva, imunohistochémia, terapia

Summary: Langerhans cell histiocytosis (LCH) is a rare proliferative disorder of Langerhans cells with uncertain etiology, wide spectrum of clinical symptoms and varied behavior. Treatment is not well defined and is highly individualized. The difficulty of the therapy also lies in the unpredictability of the clinical course. Further clinical studies are required to establish the natural course and prognostic factors of this disease and more research needs to be conducted to understand the pathogenesis and rational management of this disorder. The authors present a review of vulvar localization of LCH, and the current concept of Langerhans cell biofunction is also outlined.

Key words: Langerhans cell histiocytosis, vulva, immunohistochemistry, treatment

INTRODUCTION

Langerhans cell histiocytosis (LCH) encompasses a group of diverse disorders that are typically characterized by the accumulation and infiltration of monocytes, macrophages, and dendritic cells in the affected tissues. The clinical presentation in this group of disorders varies greatly, ranging from mild to life threatening.

Although nearly a century has passed since the recognition of histiocytic disorders, their pathophysiology remains an enigma. LCH may affect patients of any age.

The exact adult disease incidence is unknown, but is much more common in children. The estimated pediatric incidence is approximately 3-4 per million with a peak between 1 and 3 years (1). The estimated total mortality of LCH is approximately 3% in adults and 15% in children (2). Most reports are based on a single-specialty experience and there are only a few describing relatively large series of patients (3).

TERMINOLOGY

Langerhans cell histiocytosis (LCH), also known as Langerhans cell granulomatosis or histiocytosis X was first described by Paul Langerhans in 1868 (4).

Lichtenstein originated the term histiocytosis X in 1953 to describe a group of poorly understood diseases that differed in presentation but had a common pathologic characteristic: histiocyte proliferation (5).

In 1987, the International Histiocyte Society changed the name of the disease from histiocytosis X to Langerhans' cell histocytosis (6).

Patients with LCH can have a broad spectrum of disease manifestations, from involvement of a single site to widespread systemic involvement. This spectrum of clinical presentations has led to a number of terms for LCH.

Eosinophilic granuloma refers to disease limited to a single site, usually bone. Patients with Hand-Schűller-Christian disease present with a classic triad of multiple bone lesions, exophthalmos, and diabetes insipidus. Abt-Letterer-Siwe disease is an acute, progressive, and often fatal multisystem variant of LCH that usually affects the very young. There may be transitional forms between the three entities from the outset or during the evolution of the disease (7).

PATHOGENESIS

Although the clinical and histological aspects of LCH are well established, the cause and pathogenesis of LCH remain unclear. Infectious agents and cellular and immune system dysfunction, whether related to lymphocytes and cytokines, genetic factors, cellular adhesion molecules, or a combination of these, have been implicated in the etiology and pathophysiology of these disorders.

LCH is a disorder of Langerhans cells (LC). LC are dendritic, peripheral, antigen-processing cells of bone marrow origin. They present various environmental, viral, and tumor-associated alloantigens to immunologically competent T-lymphocytes, stimulate allogeneic and syngeneic mixed leukocyte reactions, secrete interleukin-1, function as accessory cells in the generation of cytotoxic T-lymphocytes, and are target cells for the generation of delayed hypersensitivity reactions and possibly for cytotoxic T-lymphocytes in acquired immune deficiency syndrome. Thus, Langerhans cells constitute an important part of the afferent limb of the localized immune response (8, 9, 10). These cells are found throughout the body but are primarily located in the suprabasal layer of human epidermis (11).

LC act as sentinels. They recognize, internalize, and process antigens encountered in the skin. Upon encountering antigens, LC become activated with subsequent maturation and induction of their migratory capacity. Activated LC then detach from their surrounding epidermal microenvironment and travel to draining lymph nodes via afferent lymphatics, where they are termed interdigitating dendritic cells. Once in the lymph node, LC lose their ability to take up and process

antigen, but instead acquire immunostimulatory capabilities. These capabilities include: upregulation of MHC molecules, expression of B7 molecules, necessary for naïve T lymphocyte activation, and the upregulation of several adhesion molecules, important for interactions with antigen-specific T cells. In this way, LC are able to process and present antigens encountered in the skin to naïve T lymphocytes in the draining lymph nodes. Maturation into functional LC is affected by cytokines such as GM-CSF, IL-1, and TNF-α (12-16).
The disease is believed to result from a disorder of immune regulation (17).
Langerhans cells in patients with LCH are aberrant and profoundly differ from normal LC. They differ from their normal counterparts in their migration, efficiency of antigen presentation, cytokine production, and expression of important cell surface proteins. LCH cells can accumulate in organs that are outside of the normal physiologic distribution of LC cells. Langerhans cells normally reside only in skin, lymph nodes, or thymus. LCH cells may also involve the abnormal accumulation of dendritic cell progenitors, which are CD34+. In a small study, the percentage of CD34+ cells isolated from the peripheral blood of patients with LCH was three times higher than in normal controls (18).
Whether LCH is reactive or neoplastic is even debated, and several features provide seemingly contradictory evidence on this point: spontaneous resolution of disease on the one hand and clonality of lesional LCH on the other (19, 20).
Like cancer, LCH can affect any organ system. LCH is not regarded as a „conventional" malignancy. Histopatologist describes Langerhans' cell „accumulation" or „activation" rather than „proliferation" important difference from true malignancy. Even studies of clonality may yield puzzling results, with some reports examining only one sample per patient and therefore showing evidence of LCH cell monoclonality in some forms of the disease (21) whilst others have reported polyclonality, when distinct lesions of the same patient have been studied at the same time (22).
The alternative possibility of LCH arising from somatic mutations that cause clonal expansion of Langerhans cells or their precursors has been proposed. However, this theory also may involve a viral theory in which viral nucleic acids give rise to such mutations, but the search for viral cause and for molecular abnormalities are still unsuccessful (23, 24, 25).
Concept of clonality in LCH remains controversial (26).
Several important insights have recently been made, which support the hypothesis that LCH is a neoplasia of dendritic cells (22).
The observation that around 1% of cases of LCH have another affected relative, either child or adult, suggests a genetic predisposing factor (27).
Therefore, each theory should not be considered to be mutually exclusive.
LCH can be progressive and fatal. In other cases, LCH is localized and self-limited. The natural history of this disease is atypical and often fluctuates. Its systemic manifestations include weight loss, fever, chills, and fatigue (28).
LCH is practically the only known human disease of dendritic cells, whose key immunological role, especially in cancer surveillance, is now of considerable interest. The importance of a methodical approach is that it may not only throw light on a disease process, but also on the physiological function of the normal cell counterpart (29).

GENITAL INVOLVEMENT

LCH of the lower female genital tract was first reported in a 6-year-old child by Lane and Smith in 1939. This case was in association with diffuse cutaneous and multiorgan involvement (30).
Localization of LCH in the female genital mucosa is rare, and Axiotis et al reviewed 42 cases in which the lesions, which were often multiple, preceded systemic evidence by many years. The age at onset ranged from 8 months to 85 years, average 29 years. LCH may encompass the vulva, vagina, cervix, endometrium, and ovary (31). These authors classified genital LCH into four distinct nosologic groups, based on initial clinical presentation and natural history:
(a) LCH of only the genital tract, (b) genital LCH with subsequent multiorgan involvement, (c) oral or cutaneous LCH with subsequent genital and multiorgan involvement, and (d) diabetes insipidus with subsequent genital and multiorgan involvement (31).
There appears to be no correlation between the histology and the outcome of the genital lesions. Complete regression, partial improvement, persistent lesions, and recurrences were seen in all four groups of patients.
Genital LCH as the sole manifestation of this disease is very unusual (32).
„Pure" vulvar Langerhans cell histiocytosis is a rare presentation. To date, 19 cases of isolated (localized) vulvar LCH have been reported (33, 34). Clinical follow-up of these cases showed that one third of the patients developed disseminated disease. The most common sites of dissemination were bones, including the sella turcica causing diabetes insipidus. Other sites of dissemination included skin, lung, oral cavity, bone marrow, and other sites in the female genital tract. Prognostic conclusions could not be drawn in this patient series due to a lack of documentation of patient follow-up.

CLINICAL PRESENTATION OF VULVAR LCH

Vulvar LCH may mimic various neoplastic and non-neoplastic disorders. Pruritic, erythematous lesions resemble eczema, seborrheic dermatitis, or Darier's disease.
Papular lesions with ulceration may resemble chancroid, granuloma inguinale, or lymphogranuloma venereum. Single indurated ulcers can have the appearance of syphilitic chancres, tuberculosis, Crohn's disease, or squamous cell carcinoma. Painful multiple ulcerovesicular lesions may be mistaken for herpes genitalis, erythema multiforme, or Behcet's syndrome. When the lesions are projecting, multicentric masses, the differential diagnosis also includes malignant melanoma and sarcoma. The rare, diffusely, indurated lesion clinically mimics Paget's disease of the vulva (32, 35-39).

DIAGNOSIS

The diagnosis of LCH is based on histopathology pattern in biopsy specimens showing multinucleated Langerhans' cells, histiocytes, and eosinophils. The presence of Birbeck granules on electron microscopic examination or the antigenic markers that react with Cd1a glycoprotein and the cytoplasmic protein S-100 detected by immunoperoxidase staining is considered diagnostic (4, 8, 40).
Strict diagnostic criteria have been published by the Histiocyte Society (6): Fresh-tissue biopsy is required to diagnose the disease. In order to establish a definitive diagnosis, either Birbeck's granules must be identified on electron microscopy or the cells must be CD1a-positive. Birbeck's granules are pentalaminar cytoplasmic inclusion bodies that sometimes have a dilated terminal. A less certain diagnosis can be made if biopsy reveals characteristic morphology and if two or more of the following are present on staining: characterictic peanut lectin binding, S-100 protein, alpha-D-mannosidase, and adenosine triphosphatase.
The differential diagnosis of LCH at the microscopic level includes immunodeficiency syndromes with graft-versus-host disease, viral infections, and infiltrative diseases such as leukemia or lymphoma, reticuloendothelial storage diseases, Erdheim-Chester disease, and papular xanthomas (41, 42).

It seems possible that LCH involving the vulva has been under-diagnosed in the past, considering that almost all cases of isolated vulvar LCH have been reported within the past twenty years. Increased awareness of isolated LCH involving the vulva and other sites in the gynecologic tract is one likely explanation for these cases being reported during the past two decades. The availability of immunohistochemical analysis for routinely processed tissues, which became widespread in the 1980s, also is a likely explanation.
It is important to exclude systemic disease in any patient suspected of having vulvar LCH. The routine evaluation should include measuring serum electrolytes and performing a chest X-ray, CT of the abdomen and pelvis, and skeletal survey (43).

TREATMENT OF VULVAR LCH

The course of LCH is unpredictable. In some cases, it resolves without treatment.
On the other hand, it can recur even after the initial response to treatment was successful. Due to the rarity of this disease, treatment of vulvar LCH is still very diverse and is highly individualized.
Therapeutic options include surgery, topical and systemic steroids, topical nitrogen mustard, radiotherapy, chemotherapy (mechlorethamine, etoposide, methotrexate, cyclosporine, vincristine, vinblastine), photochemotherapy and other treatment modalities (trimethoprim-sulfamethaxazole, isotretinoin, interferon, thalidomide) (43-47). Mixed results have been obtained with all treatment modalities.
Voelklein et al. report the case of a 36-year-old woman who presented with a 9-year history of vulvar lesions. The diagnosis of LCH was established by immunohistochemical techniques. The patient received radiotherapy to the vulva and responded with complete remission (39).
Pather et al. presented a case of isolated vulvar LCH that was initially treated with an excision biopsy but recurred 2 months later. Local vulval radiotherapy resulted in complete resolution of the lesion and there was no evidence of recurrence after 24 month of follow-up (35).
Borglin et al, Dadey and Hurxthal performed vulvectomy on the patients with vulvar LCH as initial therapy(48, 49). Also the case of Chauffaile et al support the recommendation for the primary surgical resection of the vulvar histiocytic lesions (50).
It seems that local excision of LCH nodules isolated on the vulva has the best therapeutic benefit in adult patients but 50% of the patients with genital LCH who underwent surgical excision relapsed after surgery (51). If LCH indeed has its origin in the bone marrow, then it is hardly surprising that such a high relapse rate exists.
Santillan et al. referred a 33-year-old women with isolated vulvar LCH. The patient was treated with external beam radiotherapy to the vulva after excision biopsy. The recurrence on the vulva was treated with radical vulvar excision. The second recurrence in the perineum was successfully treated with thalidomide (46).
Isolated vulvar LCH has the potential for aggressive clinical behavior, either as local recurrence or disseminated disease. Two patients of LCH primary involving the vulva presented by Padula et al after dissemination of the disease were treated with radiation therapy, vulvectomy and thalidomide (34).
Montero et al advocate in the treatment of genital LCH the use of immunomodulatory agents (thalidomide, trimethoprim-sulfamethoxazol, interferons, retinoids) as initial first-line therapies, rather than surgical excision or radiotherapy (51).
The first case of the successful use of thalidomide for genital LCH was reported by Gnassia et al in 1987 (52).
Dramatic responses of cutaneous and ano-genital lesions to thalidomide and interferons have been reported. Interferon α and β, as well as isotretinoin, have been used in cutaneous disease with some reports of lasting remissions, and should be further investigated as potential therapies for genital LCH (53).
The efficacy of thalidomide in treating several inflammatory skin diseases suggests that the mechanism of action is related to immune modulation, cytokine inhibition, and/or anti-angiogenesis. The reason for its use to treat LCH is that thalidomide is an inhibitor of tumor necrosis factor, which plays a prime role in generating Langerhans' cells from their CD34+ bone precursors (54).
Several investigators found thalidomide to be effective in treating cutaneous and genital LCH, but the response was temporary, and disease recurred after treatment ended (55, 56).
Optimal treatment has not yet been determined. New treatment modalities are needed for this disease. Large scale, clinical control, randomized trials to assess optimal therapy generally are not feasible in such an uncommon disease with variable clinical features and natural history. The difficulty of the treatment also lies in the unpredictability of the course of LCH. The establishment of the International Histiocyte Society Registry was the first step towards a cooperative effort in the management of LCH (57).

CONCLUSION

Although the occurrence of LCH on the vulva is very unusual, gynecologists must bear this possibility in mind when a woman presents atypical chronic lesions on the genital mucosa. The clinical diagnosis is impossible to establish because no typical lesions are found. In such cases, it is necessary to perform a biopsy on the mucosa, rule out the possibility of systemic disease, and review the patient periodically in order to forestall a possible spread of the disease at any time.
Its etiology and pathophysiology, as well as the most effective modes of therapy, remain elusive. More research needs to be conducted so that we may better understand the mechanisms of LCH and help to predict when the disease is benign and may resolve on its own, and when it is aggressive and unremitting and requires treatment.

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