

Langerhans Cell Histiocytosis in Childhood: Review, Symptoms in the Oral Cavity, Differential Diagnosis and Report of One Case

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Abstract

Background

Langerhans cell histiocytosis (LCH) is a rare disease in which monoclonal migration and proliferation of specific dendritic cells is seen. The disease primarily affects the bones and skin, but there is a possibility that involves other organs or appears as a multi-systemic disease.

Case Report

In oral examination of a nine-month girl, two deep wounds with a yellow membrane with approximate size of 1 × 1 cm on both sides of mandibular alveolar ridge were seen. The edges of the wounds were swollen and proliferated and redder than the surrounding mucosa. At the touch the edges of the wound were not indurated. The wound were created from the third-month and the size of wounds had become slightly larger within 6 months. According to the chronic wound and being non-responsive to various systemic and local treatments, incisional biopsy was taken from the wounds. Langerhans cell histiocytosis was confirmed histologically and immune histochemically.

Conclusion

Mouth ulcers may be the only symptoms of Langerhans cell histiocytosis. Therefore, the role of dentist could be important in diagnosis of this disease.

Key Words: Bone lesions, Granulomatous gingivitis, Infants, Langerhans cell histiocytosis, Periodontitis.

*Please cite this article as: Mohammad Shooriabi, Mohsen Parsazade, Shahram Bagheri, Seyed Amir Razavi Satvati, Roohollah Sharifi. Langerhans Cell Histiocytosis in Childhood: Review, Symptoms in the Oral Cavity, Differential Diagnosis and Report of One Case. Int J Pediatr 2016; 4(8): 3343-53.

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Received date Feb23, 2016; Accepted date: Mar 22, 2016

1- INTRODUCTION

Histiocytic disease in adolescents and adults includes three main classes including dendritic cell disorders, disorders of macrophages and histocytes malignant disorders (1). LCH is included in dendritic cell disorders and caused by clonal proliferation of LCH cells (which are round shape and are immunophenotypically and functionally immature) associated with eosinophils, macrophages, lymphocytes and sometimes multi-nuclear giant cells (2). Langerhans cells are immature dendritic cells in LCH lesions that comprise less than 10% of cells in LCH lesions (3, 4). The term LCH cells is used, because there is a significant difference morphologically, phenotypically and in gene expression between epidermis langerhans cells and those that are in LCH lesions (5-7).

In the present, the use of the term Langerhans cell histiocytosis is preferred to histiocytosis X, eosinophilic granuloma, Abt-Letterer-Siwe disease, Hand-Schuller-Christian disease or diffuse reticuloendotheliosis, because it has been observed that histocyte pathological cells, which can be seen in all the diagnosis mentioned above have the same immunophenotypic characteristics that the existence of Birbeck granules could be noted (8, 9). In addition, pathological histocyte or LCH cell has gene expression profile very similar to myeloid dendritic which there is higher probability that the origin of LCH cell is from progenitor cells in blood circulation than skin langerhans cells (9). Nevertheless, in 60% of LCH biopsy samples are indicated V600E mutation in BRAF oncogene (regardless of stage of disease or organ involved). This discovery is led to the conclusion to know LCH more as a neoplastic disorder (10, 11). LCH is classified clinically into the three groups of localized single-system disease, multifocal single system disease and multisystem disease. The involvement

location has prognostic importance, so that the involvement of liver, spleen and bone marrow are considered as involvement of high-risk organs and the involvement of skin, bone, lung, lymph nodes, gastrointestinal ducts, pituitary gland, and central nervous system, are considered as low risk organs (1, 7).

The unifocal form is usually benign, affects older children and adults and is characterized by a solitary bone lesion, usually in the skull or spine (12). Less frequently, this form affects lymph nodes, skin, or lungs. According to the older terminology, the unifocal form corresponds to eosinophilic granuloma.

Multi-focal form of LCH (was called Hand-Schüller-Christian disease in the past), is more invasive and affects infants and several bone lesions and involvement of the adjacent soft tissue are seen in it. Multi-system and disseminated multi-focal LCH (which was called Abt-Letterer-Siwe disease in the past) has undesirable prognosis and affects infants and is appeared in skin, lymph node, gastrointestinal ducts, bones, and with less prevalence in central nervous system. Clinical signs of disseminated form of LCH are expressed by lack of appetite, growth failure in children, weight loss, fatigue, high temperature, upper respiratory tract and middle ear infections (13). The incidence of LCH is 8.9 per 1 million children below the age of 15 years old. Generally, the age of children at the time of diagnosis is three years old (14). The male to female ratio is almost one. Living in crowded environments and low economic status was associated with an increased risk of LCH (15). Osteolytic lesions in the jaw's bone occur more in posterior mandibular area and it could cause inflation of the soft tissue, pathological fracture of the jaw and teeth loosening and premature falling of the teeth. Typical radiographic changes in LCH are seen as single or multiple osteolytic

lesions with irregular border. Osteolytic lesions may have sclerotic margin (7). The most common skin lesions are seborrheic eczema that occurs typically in infants and neonates in the form of disseminated red to brown papules that are wounded in the center. Dermatitis may rarely be associated with the dystrophic changes of nails. Individual skin lesions usually have a good prognosis and a 60 percent of recession. However, the exact monitoring of lesions must be performed, because reactivation of lesions or their progress and involvement of several systems have been seen in 40 percent of the patients (7, 14).

Typical histopathologic findings involve dense infiltration of langerhans cells, macrophages, lymphocytes, eosinophilic granulocytes and giant cells. Langerhans cells have quite large eosinophilic cytoplasm and irregular nucleus, often with a groove (coffee beans) (16).

In the case of using immunohistochemistry may CD1 which is an antigen on the surface of langerhans cells and also, S100 appear (17). At the time of diagnosis a full work-up should be done to determine the extent of the disease and risk-based therapy to be traced. Work-up should be consisted of the exact history and physical examination, complete blood count, metabolic panel including function tests of kidney and liver, bone scan, skeletal survey and chest radiography. Urine analysis should be done to assess insipidus diabetes probable involvement of hypothalamic pituitary. Further analyses such as water deprivation test, antidiuretic hormone levels or other endocrinological examinations that assess function of pituitary-hypothalamus dependent to the patient's clinical symptoms may be essential. Due to the rarity of the disease and the diversity of location, type and severity of the disease, it is not provided any clear guideline on the treatment of LCH. LCH as multi-focal or multi-system often needs more severe treatments like

chemotherapy. Articles that describe the management of the unifocal bone lesions propose various treatments such as observation, surgical curettage, radiation therapy, steroid injections, and chemotherapy, or combined therapy with two or more than two drugs (18- 20).

2- CASE REPORT

Nine-month old girl was referred by a general dentist to Department of Oral Medicine, Faculty of Dentistry, Ahvaz Jundishapur University of Medical Sciences, Ahvaz city, Iran. Dentist had referred the patient for diagnosis and treatment of mouth ulcers. The parents were healthy and there was no significant point on their medical history. The patient was the first child of parents who were born after ten years of the marriage. Pregnancy period was complete and the maternity had been done by normal delivery. The child nutrition was by breast feeding. The child's weight at the time of visiting was 7.5 kg and her height was 80 cm. The child's mother declared that the wounds has been created from about when she was three months old symmetrically in the both sides of the patient's lower jaw and is slightly larger over the time. For the treatment, oral ketoconazole, benzydamine and chlorhexidine mouthwash, nystatin suspension prescribed by different physicians that had no effect on mouth ulcers. The child's mother rejected any fever, allergy and feeding difficulties in her child.

In physical examination the patient was well developed and well nourished and there was no sign of acute distress. The child has no fever and her vital signs were within normal range. General physical exam was normal. Except the inside of the mouth the rest of the head and neck examination was normal. In the oral cavity, there were major changes on the alveolar mucosa of the toothless lower jaw. The lesions were located bilaterally in

the distal parts of the alveolus in the form of deep ulcerations covered by fibrin by roughly one-on-one centimeter. The border of the wounds was bold and proliferative and red and in touching the borders of the wound, were non-indurated (**Figures 1 and 2**). The rest of the oral mucosa was normal. According to the chronic wounds for a 6 months period and suspicion to LCH and malignant lesions, biopsy were taken individually from the both wounds under general anesthesia in the hospital and sent to the laboratory for

histopathological study. In hematoxylin eosin test, LCH is suspected (**Figure.3**) that in Immunohistochemistry (IHC) was confirmed for S100 and CD1a (**Figures 4 and 5**). Finally, patient was referred to the oncology department of the Golestan hospital in Ahvaz for the treatment. Laboratory findings such as complete blood count (CBC), biochemistry of the blood, urine analysis, urine anillylmandelic acid (VMA), liver and kidney function, bone scan, radiography from chest and γ -scan were normal (**Figures 6 and 7**).



Fig.1 and 2: Bilaterally oral ulcer in the distal parts of the mandibular alveolus

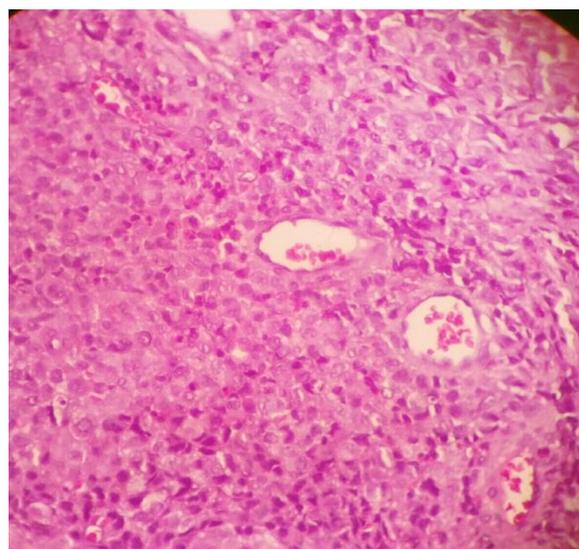


Fig.3: High-power view showing infiltrate of Langerhans cells and eosinophils (stained with haematoxylin eosin)

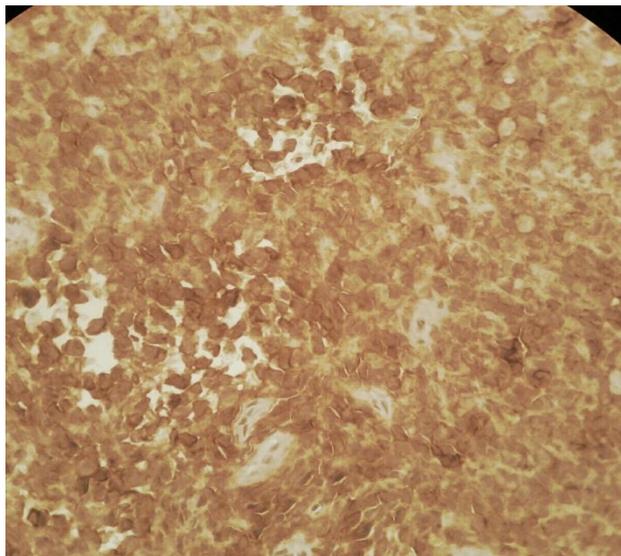


Fig.4: Langerhans cells showing immunohistochemical positivity of CD1a

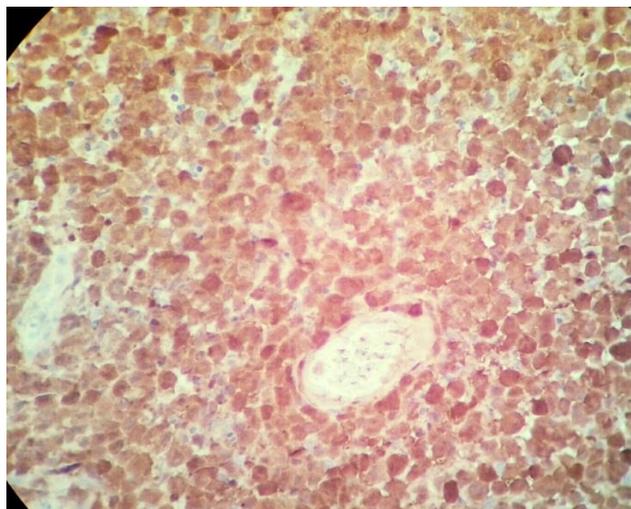


Fig.5: Langerhans cells showing immunohistochemical positivity of S100 protein

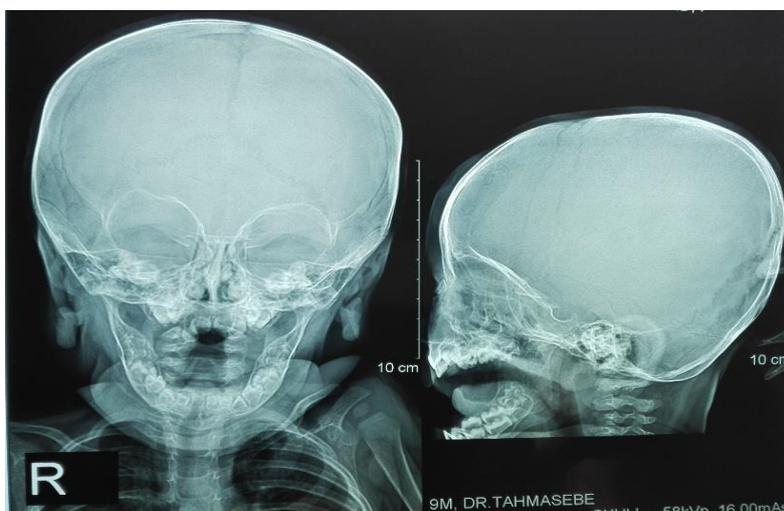


Fig.6: Head radiography

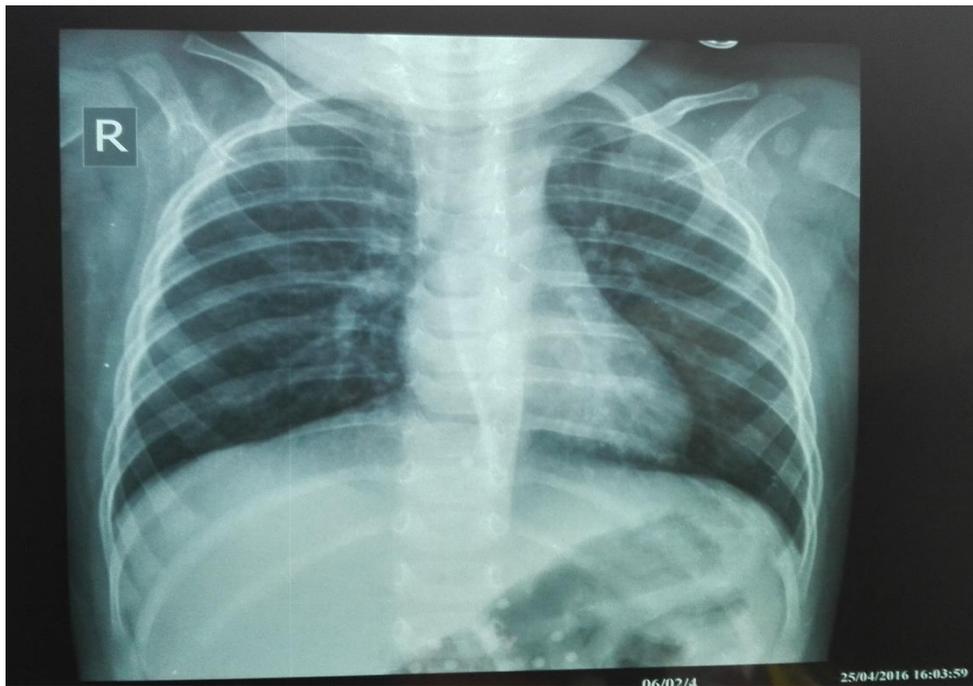


Fig.7: Chest radiography

3-DISCUSSION

Histocytic diseases are a group of disorders that include a wide range of the benign and malignant, multiple and single, primary and secondary diseases and because of the common origin that is histocyt are included in the same category (1). LCH belongs to the dendritic cell disease and is the most common in the children (**Table.1**).

Although, LCH could cause lesion in any bone, but the previous studies have showed that head and neck are the most common anatomical locations that LCH bone lesions appear (8). So that, the incidence of lesion in the skull (especially calvarium, temporal bones and sella turcia), and maxilla or mandible is 65-90% (17). Also, mandible is involved more than maxilla (21). Single bone lesions may improve spontaneously over the several months or years. It has been seen that biopsy from bone lesions without radical excision, may lead to accelerated healing process of the lesion (15). In multi-focal bone involvements, systemic therapy by

prednisone and vinblastine may be considered (10). Oral involvement in LCH is a common finding that may be seen as enlargement of the gums, oral ulcers, tooth mobility, jaw pain, facial swelling, Osteolytic lesions of bone and scooped out radiolucency's of the alveolar process (22). These oral cavity symptoms may be first and even the only sign of LCH (23). In periodontal tissue, erosions or elliptic wounds with tumorous erythematous margin is seen which in touch is painful and causes tooth mobility, gingival and periodontal pockets.

Deep periodontal pockets are seen in mouth cavity that it is considered because of the jaw destruction. This causes teeth mobility and makes a profile called "teeth floated in the air" that could result premature loss of primary teeth. Infiltration of the gum causes of granulomatous gingivitis (8). Mucosal lesions appear as round or elliptic wounds with swelled margin and erythematous which are painful in touch. In rare cases, mucosal lesions of the mouth could be seen in lack of the bone lesions (23). In our

patient, pathological lesions are seen symmetrically in distal mandibular alveolar ridge. In X-ray of patient, bone lesion was not observed and it seems that mucosal lesions were without bone involvement (8, 24, 25). The incidence of mouth lesions in LCH is 77% (26), therefore, in some patients primary diagnosis may be done by the dentist (27). Bartnick in order to treatment planning and determining the prognosis of LCH in maxillofacial area suggested that the disease be staging as the following: patients with one single lesion is placed in stage I and patients with several lesions in stage II. Patients that in addition to involvement of orofacial area simultaneously, have pathological changes in other organs are placed in stage III.

Along with this division, it is necessary to consider whether the lesions are found only in the bone, only in the soft tissues, or in the internal organs. Stages 1 and 2 have the most desirable prognosis when only the bone or soft tissue is involved (25). Accordingly, our patient was stage 2 and has a good prognosis.

Unifocal lesions usually don't need treatment, because they may spontaneously disappear. While, multifocal and disseminated lesions may need a combine of several treatment method including surgical curettage. Some of the authors have suggested radiotherapy with low dose for multi-focal or large lesions that have recurrent or have progressed following the surgery, lesions that are not available for surgery, painful or disseminated lesions or lesions that occur in ossification centers of the mandible during infancy. It seems a dose of 600 to 1000 cGy in three to five sessions could make the local control of the disease in most patients. Due to the possibility of damage to permanent teeth follicles and the risk of cancer development and effect on the growth especially in children, using this method is reduced (12, 28, 29).

At the beginning of the disease or even at the reactivation of multisystem LCH, combination of vinblastine and low dose steroid is very effective in most of the patients. Also, low-dose steroids for 4 weeks, followed by short pulses three-weeks apart, do not induce undesired, cushingoid toxicity. Therefore, this combination therapy is still recommended as the first line of the treatment of multi-system LCH in children, with the aim of limiting the disease and its resulted complications. In refractory cases, the combination of cytarabine and cladribine has been presented as the second line treatment (1, 8, 22, 23, 28).

In the differential diagnosis (**Table.2**), it's necessary to consider some benign and malignant bone lesions, and also, oral mucosal disorders and periodontal tissue. The diseases that may occur with similar appearance to LCH include: prepubertal periodontitis, leukemia, neutropenia, hypophosphatasia, fibrous dysplasia, and Papillon-Lefèvre syndrome (PLS) (22).

The prepubertal periodontitis is related to *Actinobacillus actinomycetemcomitans* and may cause to teeth loose and destruction at the age of three. The distinction of this state from LCH is based on limited gingival inflammation with marginal bone loss and observation of *Actinobacillus Actinomycetemcomitans* in subgingival culture (30). Acute myelogenous leukemia may occur as gingival hypertrophy and similar to LCH. Acute Myelogenous Leukemia (AML) includes 15 percent of leukemia in children. The disease is confirmed by systemic symptoms in AML patients and the results of bone marrow aspiration (22, 31). The different neutropenic disorders may lead to severe gum inflammation and bone loss; and the reduction of neutrophils numbers may be due to the defects in the production of neutrophils in bone marrow or destruction of neutrophils. This state is usually associated with systemic

symptoms such as splenomegaly and infection, and distinguished from LCH by the laboratory tests (32). Hypophosphatasia is characterized by low serum alkaline phosphatase levels and excessive excretion of phosphoethanolamine in the urine, and its classic oral finding is different from LCH. Premature loss of primary teeth (which often have abnormally large pulp spaces) begins from anterior mandible region in hypophosphatasia (22, 33).

Fibrous dysplasia is a non-neoplastic progressive expansile bony lesion that may lead to premature loss of primary teeth. Facial swelling causing to "eyes-raised-to-heaven" or cherub look is the way to distinguish this state from LCH (34). Papillon-Lefèvre syndrome is associated with specific alveolar bone destruction and premature loss of primary teeth. This state is distinguished from LCH by hyperkeratosis of palms and soles (35). Seborrhic skin lesions or atopic dermatitis is typically appeared in children with LCH

(in 38% of patients) and is between the first LCH presentations. Skin changes are seen in the inguinal region, perineum, abdomen, the axillary region, neck, scalp, and the lumbosacral region. Skin lesions are like reddish-brown papules which can be seen in depigmentation area after recovery. In some cases, the scar appear on the skin. There were some children that had typical skin changes, but mistakenly were treated as atopic dermatitis, and after a while, the diagnosis of LCH was confirmed for them (36, 37).

LCH does not include typical characteristics of malignant diseases, and also, it is not followed by metastasis (8). However, predicting how it develops is difficult and while some patients are recovered without any treatment, the disease spreads to other organs, causing defects in that organ and leading to fatal consequences. LCH permanent complications include diabetes insipidus, exophthalmos, and orthopedic problems (38).

Table 1
Current classification of the histiocytic disorders.

Dendritic cell disorders	Langerhans cell histiocytosis Secondary dendritic cell processes Juvenile xanthogranuloma Solitary histiocytomas with a dendritic phenotype
Macrophage-related disorders	Primary and secondary hemophagocytic syndromes Rosai-Dorfman disease Solitary histiocytoma with a macrophage phenotype
Malignant histiocytic disorders	Monocyte-related leukaemias Extramedullary monocytic tumour Dendritic cell or macrophage-related histiocytic sarcoma

Table-2: Differential diagnosis of LCH (From Madrigal-Martínez-Pereda C, Guerrero-Rodríguez V, Guisado-Moya B, Meniz-García C. Langerhans cell histiocytosis: Literature review and descriptive analysis of oral manifestations. *Med Oral Patol Oral Cir Bucal.* 2009 May 1;14 (5):E222-8).

Oral mucosa lesions	Parodontitis			
	Submucous abscess			
	Subperiosteal abscess			
	Trauma			
	Necrotizing sialometaplasia			
	Tuberculosis			
	Deep mycotic infection			
	Melanoma			
	Papillon–Lefèvre syndrome			
	Cyclic neutropenia			
	Hypofosfatasa			
	Bone lesions	Unifocal	Children	Odontogenic cyst
				Periapical lesions
Metastatic neuroblastoma				
Infrabony haemangioma				
Fibrous dysplasia				
Epidermoid cyst				
Giant cell granuloma				
Haemophilic pseudotumor				
Osteolytic metastasis				
Multiple myeloma				
Multifocal		Adult	Myxoma	
			Ameloblastoma	
			Osteogenic sarkoma	
			Fibrosarkoma	
			Osteomyelitis	
			Ewing's sarcoma	
			Brown tumour in hyperparathyroidism	
			Multiple odontogenic keratocyst	
			Multilocular cyst	
			Leukaemia	
Lymphoma				

4-1. Limitations of the study

Despite few articles on this topic, restrictions to access the papers, this review, aspires to provide further disease information regarding oral LCH.

5. CONCLUSION

Clinical presentations of LCH in young patients could primarily appear only in the mouth. They need to be treated on the extent of the disease, and require long-term care. Awareness of the symptoms of LCH in the head and neck area is

important for dentists and this is a way by which they can help early diagnosis of this serious disease.

6- CONFLICT OF INTEREST: None.

7- ACKNOWLEDGMENT

The authors appreciate the help of the Vice Chancellor of Research and Technological Development, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, for financial support of this thesis.

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