

## Indeterminate cell histiocytosis with naïve cells

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### Abstract

Histiocytoses are a heterogeneous group of disorders characterized by proliferation and accumulation of cells of mononuclear-macrophage system and dendritic cells. Histiocytoses are categorized according to the cell of origin into Langerhans cell histiocytosis (LCH), Non Langerhans cell histiocytoses and indeterminate cell histiocytosis (ICH). ICH is an extraordinary rare neoplastic dendritic cell disorder that has poorly understood histogenesis and pathogenesis. It is characterized by a proliferation of dendritic cells, which mimic Langerhans cells immunophenotypically (positive for CD1a and S-100 protein), but lack Birbeck granules characteristic of Langerhans cells. Twenty-four year-old Egyptian male was presented with reddish brown chest wall nodule. Clinical, histopathological, immunohistochemical and ultrastructural features are typical for ICH. He was in a good state without any evidence of recurrence or metastasis after 24 months follow up. Peculiar histopathological features were detected in the present case. Many unidentified cells with Hematoxylin & Eosin Langerhans like features showed negative staining for S-100, CD1a, Langerin and CD68. In absence of cellular atypia and mitosis, the infiltrating cells showed epidermotropism that was reported once in ICH as well as neural and perineural invasion that were not previously



Figure 1. Reddish brown nodule (1x1 cm) on the chest wall.

reported. Therefore we prefer using a tentatively designated diagnosis; *dendritic cell tumor, not otherwise specified* or newly proposed diagnosis (Indeterminate cell histiocytosis with naïve cells) for the present case.

### Introduction

The histiocytic disorders cover a wide range of benign and malignant diseases and can be differentiated on the basis of clinicopathologic features, ultrastructural picture and prognosis. According to the origin of the proliferating cells, these conditions have been classified as Langerhans, non-Langerhans, and indeterminate cell histiocytoses.<sup>1</sup> Indeterminate cell histiocytosis (ICH) is a rare proliferative disorder, in which the predominant cells share morphologic and immunophenotypic features from both Langerhans cell histiocytosis (LCH) and non-Langerhans cell histiocytosis (NLCH).<sup>2</sup>

### Case Report

Twenty-four years Egyptian male presented for evaluation of an asymptomatic reddish brown nodule on the anterior chest wall. Lesion showed gradual increase in size for 6 months then became stationary. Clinical examination revealed normal healthy patient with no manifestations of systemic diseases or lymphadenopathy. Dermatological examination revealed a solitary reddish brown non tender nodule measuring 1x1 cm. (Figure 1). It

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was provisionally diagnosed as solitary reticulohistiocytoma. Extensive laboratory and imaging evaluation failed to reveal any underlying malignancy or systemic disease. Nodule was totally excised after taking patient's consent.

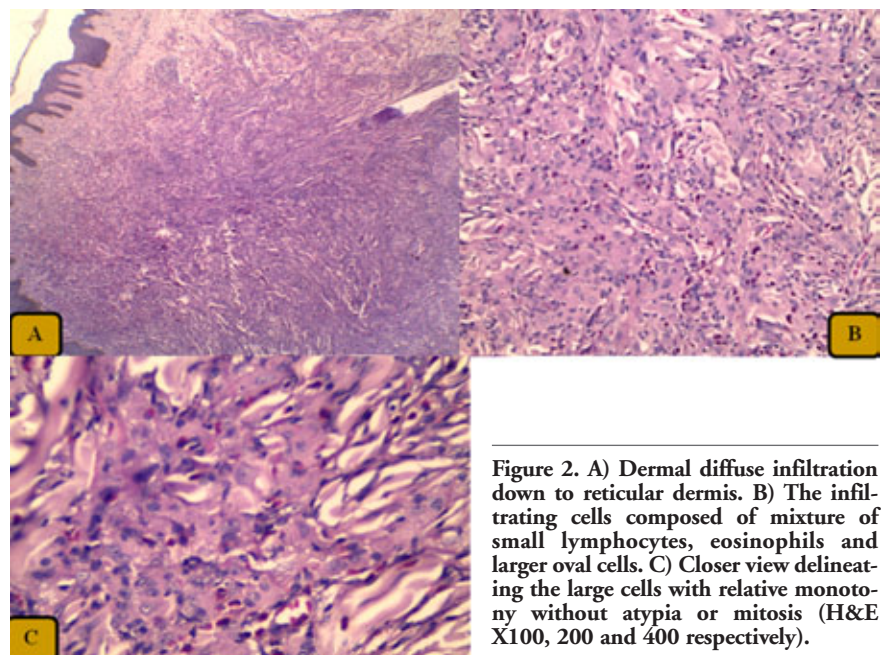
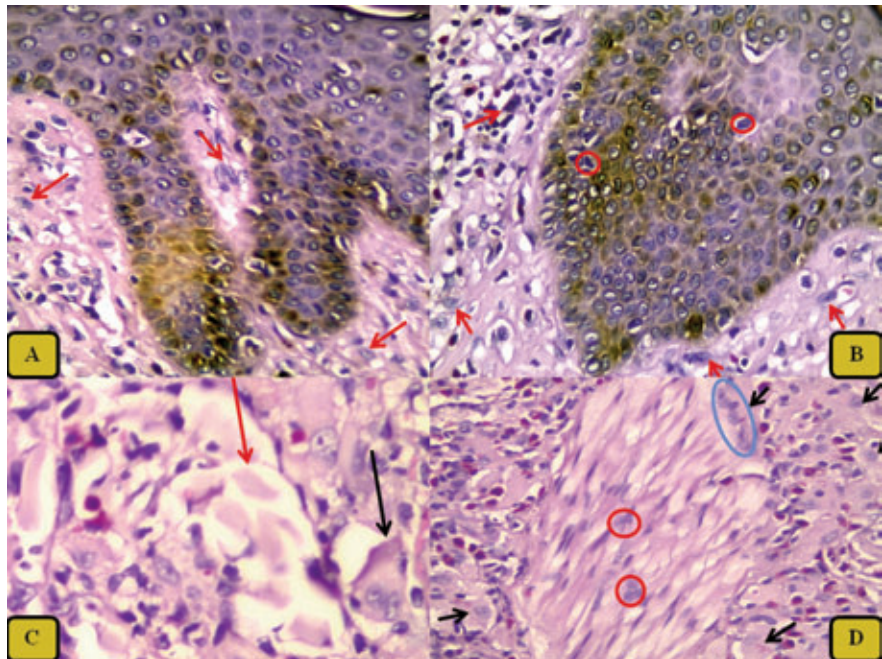


Figure 2. A) Dermal diffuse infiltration down to reticular dermis. B) The infiltrating cells composed of mixture of small lymphocytes, eosinophils and larger oval cells. C) Closer view delineating the large cells with relative monotony without atypia or mitosis (H&E X100, 200 and 400 respectively).

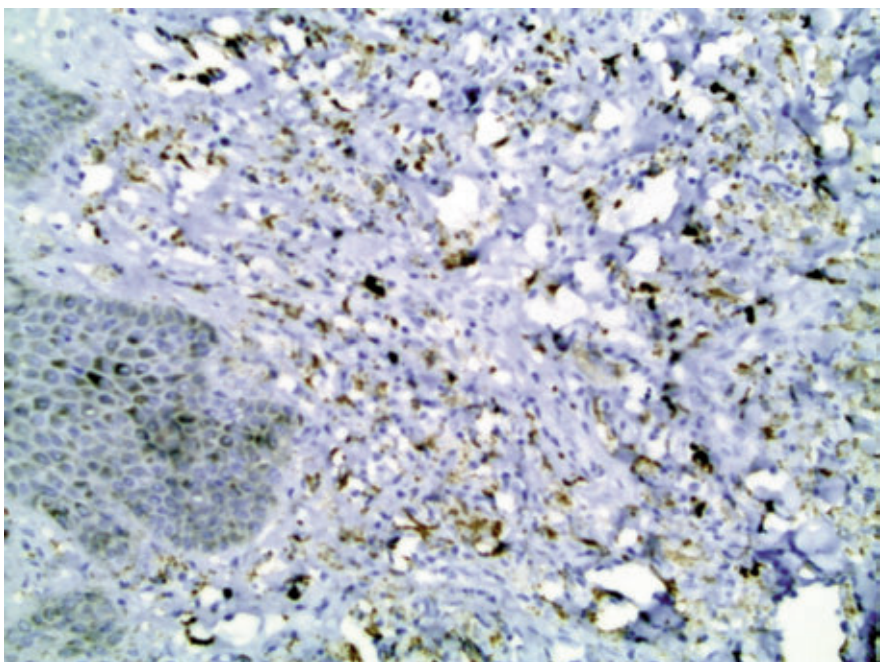
Histopathological examination of hematoxylin and eosin (H&E) stained sections revealed dermal diffuse infiltration of mixture of small lymphocytes, eosinophils and larger oval cells with abundant cytoplasm and relatively oval, folded or indented nuclei with fine chromatin, inconspicuous nucleoli and thin nuclear membrane (Figure 2A-C). Some have longitudinal nuclear grooves (Figure 2A-C). The infiltrates extended superficially to epidermis (epidermotropism) (Figure 3A, B) and deeply into the reticular dermis. Unlike the resident epidermal Langerhans cells, they are oval in shape, surrounded by a clear space and devoid of dendritic cell processes. Few multinucleated cells were present (Figure 3C) but no atypia or mitosis could be detected. Perineural and neural invasion were identified (Figure 3D). Immunohistochemical staining for S-100 showed diffuse nuclear and cytoplasmic positivity in both epidermis and dermis infiltrating cells (Figure 4). Also positive CD1a (Figure 5A,B) and CD68 (Figure 6A,B) immunohistochemical staining were detected in some infiltrating cells. However, many unidentified cells with H&E Langerhans like features showed negative staining for S-100, CD1a, Langerin and CD68. All infiltrating cells displayed negative immunostaining of CD45, CD30, follicular dendritic cell markers (CD35, CD23 and CD21), CD34 and myeloperoxidase. Ultrastructure examination revealed ovoid indented nuclei and absence of Birbeck granules (Figure 7). Given the clinical presentation, histopathological findings, immunohistochemical staining and ultrastructural findings, we confirmed the diagnosis of indeterminate cell histiocytosis (indeterminate dendritic cell tumor). Strict follow up of the patient for 24 months showed no evidence of recurrence

## Discussion

ICH was first described by Wood *et al.* in 1985 as a neoplastic disease originating from dermal indeterminate cells that are characteristically positive for S-100 and CD1a but lack Birbeck granules.<sup>3</sup> ICH seems to show no gender- or age-specific predilection.<sup>4</sup> The clinical features of this disease include either single or multiple, asymptomatic, cutaneous papules and nodules in otherwise healthy individuals.<sup>5</sup> In most cases, lesions are located on the trunk and extremities. The course of solitary ICH lesions is difficult to assess, because they are usually removed.<sup>6</sup> While most cases of ICH appear spontaneously, there are clues that some may represent reactions to triggers, such as scabies or pityriasis rosea.<sup>7</sup> In these patients, the lesions followed the distribution pattern of the prior disease.<sup>8</sup> Evidence of these diseases was lacking in our case.



**Figure 3.** A) Upper dermal infiltration by large oval cells with abundant cytoplasm and relatively oval, folded, indented or reniform nuclei with fine chromatin, inconspicuous nucleoli and thin nuclear membrane with occasional grooving (arrows). B) Epidermotropism of possible indeterminate cells with oval to elongated nuclei surrounded by a clear space in the mid epidermis and devoid of dendritic cellular process (circles) together with the same infiltrates seen at upper dermis (arrows). C) Higher power view showed the infiltrating cells, fragmented collagen bundles (red arrow) and giant cells (black arrow). D) Nerve entrapped by the proliferating cells (black arrows) admixed with eosinophils; Langerhans like cells with perineural (oval) and also neural invasion (red circles) (H&E X200 for A & B and X400 for C&D).



**Figure 4.** Diffuse strong nucleocytoplasmic positive S100 immunoreactivity in both dermis and epidermis (Immunohistochemistry X200).

Extracutaneous lesions and systemic symptoms are rare. In the literature, one infant with exclusively osseous involvement and one patient with corneal changes have been reported.<sup>9,10</sup> The main clinical differential diagnoses of a solitary lesion are juvenile xanthogranuloma and solitary reticulohistiocytoma (Table 1). However, positivity for S-100 and CD1a helped to distinguish ICH from these cutaneous NLCH disorders.

The origin of indeterminate cells gained a lot of debate. Some authors reported that indeterminate cells (IC) may represent precursors of Langerhans cells (LC) which acquire Birbeck granules as they transit from dermal to epidermal sites, possibly as a result of the interaction between their cell receptors and epidermis-specific ligands.<sup>11</sup> Another author claimed that IC belong to the family of *myeloid* cells.<sup>12</sup> Others suggested that IC represent members of the dermal/epidermal dendritic cell system that migrate from the skin to the regional lymph nodes.<sup>13</sup> Hence ICH seems to be a disorder of proliferating IC which have been locally arrested before they can leave the skin travelling as veiled cells via the lymphatics to the T-cell-dependent paracortical areas of the regional lymph nodes.<sup>4</sup> More recently, it has been suggested that what today is described as ICH could be a variant of NLCH rather than an overlap between LCH and NLCH. Authors supported their theory on basis of aberrant S-100 protein that has been reported before in cases of NLCH.<sup>13</sup> CD1a positive reactivity may also be seen in NLCH. However, this positive immunoreactivity is weak and focal, usually subepidermal, or with a starry sky background reactivity.<sup>14</sup> Other authors believe that there are disorders of LC and macrophages; both differ according to the time cycle of the lesions. Late stages of LCH may completely loss LC markers and then consist mainly of xanthomatized macrophages.<sup>15</sup> On the other hand, dermal macrophages have been shown to be capable of induction to differentiate into LC.<sup>16</sup> Furthermore, a common transitional macrophage and/or dendritic cell progenitor is believed to exist between LC, IC, and macrophages.<sup>17,18</sup> Nowadays it is not clear that ICH is a separate entity or represents various macrophage disorders identified at different periods in the inflammatory response.<sup>15</sup> Our case is of particular interest because of its unique histopathological findings. Despite of absence of cellular atypia and mitosis, the infiltrating cells showed epidermotropism that was reported once in ICH.<sup>6</sup> Unlike the resident epidermal LC, epidermotropic cells were oval in shape surrounded by a clear space and devoid of dendritic cell processes. Additionally, perineural and neural invasion were observed. To the best of our knowledge both perineural and neural invasion were not previously reported in literature. Many of the infiltrating

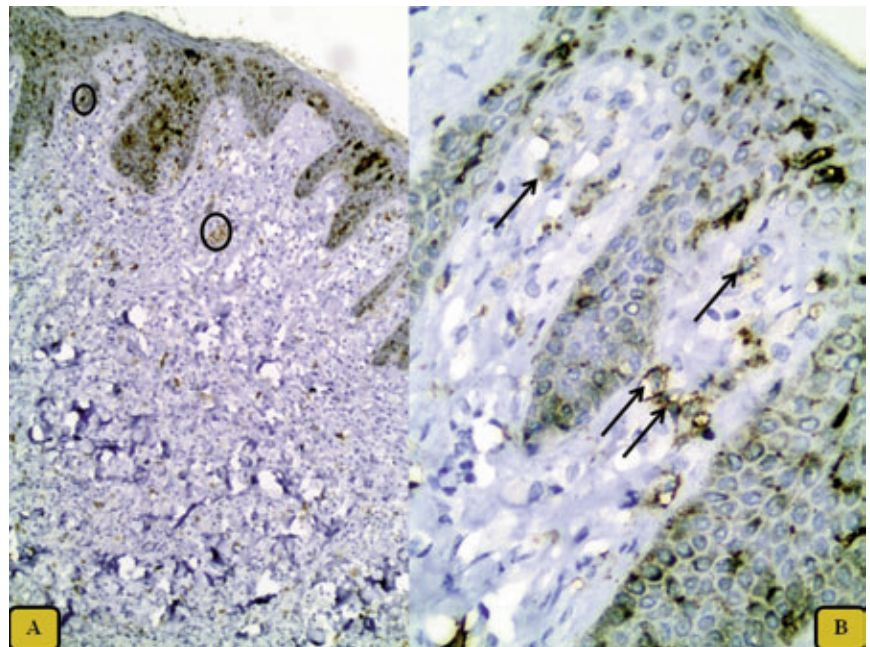
cells with LC features showed negative immunoreactivity to all assessed markers (S-100, CD1a, Langerin, CD68, CD45, CD35, CD21, CD23, CD30 and CD34). Therefore, the present case of ICH had cells displayed different patterns of immunoreactivity; population with hybrid positive immunoreactivity for S-100, CD1a and CD68 that supported the diagnosis of ICH and unidentified cell population.

The newly described cells could be the alleged precursors of LC.<sup>19,20</sup> These may be derived either from myeloid-derived dendritic cells, such as indeterminate dendritic cell tumor; or from stroma-derived dendritic cells such as fibroblastic reticular cell tumor. Additionally, these cells may be langerin -ve subset of dermal dendritic cells but absence of positivity for CD45 and CD68 do not support

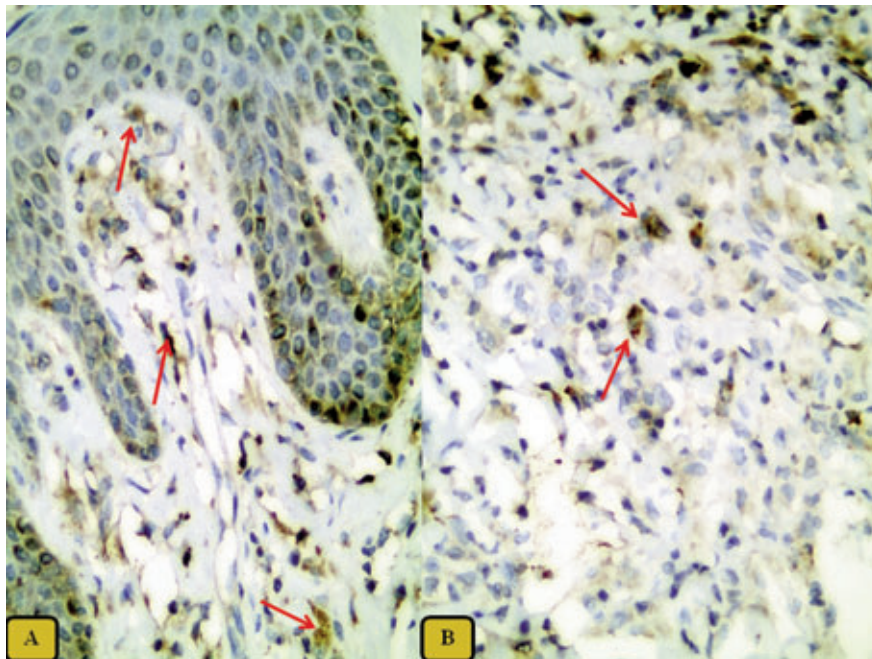
**Table 1. Clinical differences between indeterminate cell histiocytosis, juvenile xanthogranuloma and solitary reticulohistiocytoma.**

	ICH	JXG	Reticulohistiocytoma
Age	No age-specific predilection	Mainly children (1 <sup>st</sup> 2 years of life)	Adults
Gender	No predilection	Males > females	No predilection
Number of lesions	Single, multiple	Single, multiple	Single, multiple
Type of lesions	Papules, nodules	Papules, nodules	Nodules
Distribution	Trunk, extremities	Generalized with predilection for the face and upper trunk	Head
Mucous membrane involvement	-	Rare	-
Systemic involvement	Rare	Rare	-
Course	Spontaneous resolution / persistence / relapse	Spontaneous resolution	Persistent

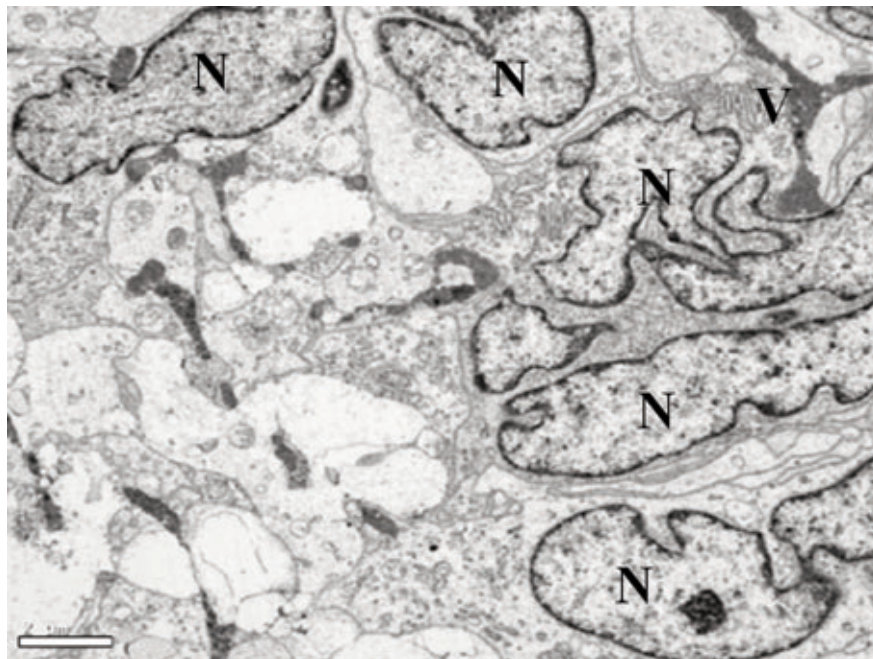
ICH, Indeterminate cell histiocytosis; JXG, juvenile xanthogranuloma.



**Figure 5. A) Positive CD1a in epidermis and dermis (circles). Note also negative staining of many unidentified cells (Immunohistochemistry X100); B) Higher power view showed positive CD1a immunoreactivity in epidermal and dermal cells (arrows), CD1a had a uniform surface with paranuclear dots pattern (Immunohistochemistry X400).**



**Figure 6.** A) Positive CD68 in some infiltrating dermal cells (arrows) (Immunohistochemistry X400). B) Other view for CD68 positive cells (arrows). Note also negative staining of many unidentified cells (Immunohistochemistry X400).



**Figure 7.** An electron micrograph showed nuclear infolding and indentation (N) with focal peripheral villous projections (V) but no Birbeck granules (Transmission electron microscopy original magnification X 4400, scale bar 2  $\mu$ m).

this hypothesis.<sup>21</sup> Other possibility for the nature of these unidentified cells is plasmacytoid dendritic cells (pDCs). Morphology of pDCs showed two opposite aspects. One type appeared plasma cell-like. Cells are round-to-polygonal with missing dendrites. The other type showed a much more dendritic shape.<sup>22</sup> In our case, the unidentified cells did not display the features of two opposite aspects of plasmacytoid DCs. In addition, frozen immunohistochemistry, flow cytometry or immunofluorescence techniques are not possible because no cryomaterial was available (as our case presented by solitary small nodule) to perform wide panel of markers. Also because these cells devoid of positivity for the first panel of markers for dendritic cell disorders (S100, CD1a, CD68), the activation and maturation DCs markers are not needed. Therefore, we depend on these facts to reach the diagnosis.

These neoplasms are extraordinary rare, and include rare types of dendritic cell tumor other than better delineated entities. However some dendritic cell tumors may remain unclassifiable despite extensive work-up or show hybrid features and such cases may be tentatively designated (dendritic cell tumor, not otherwise specified).<sup>23</sup>

Because ICH is a rare disorder and has a variable clinical course, treatment has not been established. Total excision, phototherapy, electron beam therapy, chemotherapy, electrodesiccation, topical pure coal tar, and 5% 5-fluorouracil cream have all been proposed.<sup>24,25</sup> In some patients, the process is clinically benign and may resolve spontaneously. Conservative management might be favorable for these patients.<sup>26,27</sup> However, the disease can also be extensive and debilitating.<sup>28</sup>

## Conclusions

We conclude that application of this tentatively designed diagnosis (dendritic cell tumor, not otherwise specified) or newly proposed diagnosis (Indeterminate cell histiocytosis with naïve cells) for the present case; because of the following composite features: i) epidermotropism, ii) neural and perineural invasion, iii) absence of Birbeck granules, iv) presence of naïve cells devoid of the ordinary immunophenotyping, v) presence of hybrid cells with immunoreactivity for S100, CD1a and CD68 that are suggestive of ICH and vi) excellent prognosis for 24 months follow up with no evidence of recurrence or metastasis. We recommend further studies to elicit the nature of unidentified naïve cells. Also follow up is highly recommended for patients with this unrecognized entity of histiocyte/dendritic disorder.

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