Paraneoplastic Pemphigus Associated With Castleman Tumor

A Commonly Reported Subtype of Paraneoplastic Pemphigus in China

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Background: Castleman tumor, a rare lymphoproliferative disorder, is one of the associated tumors in paraneoplastic pemphigus. We analyzed the characteristics of a group of patients with Castleman tumor to clearly understand and to improve the prognosis of the disease.

Observations: Ten cases of paraneoplastic pemphigus associated with Castleman tumor treated in the Department of Dermatology, Peking University First Hospital, Beijing, China, from May 1, 1999, to March 31, 2004, were analyzed for clinical aspects, characteristics and histologic features of the tumors, and computed tomographic findings. Literature was reviewed and data were compared with our cases. Castleman tumor was a frequently reported neoplasm in association with paraneoplastic pemphigus in China. The disease was found to be caused by an autoimmune reaction originating from the B lymphocytes in the Castleman tumor.

Conclusions: Castleman tumor in association with paraneoplastic pemphigus is a commonly reported subtype of paraneoplastic pemphigus in China. Early detection and removal of the Castleman tumor are crucial for the treatment of this tumor-associated autoimmune disease.

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In 1990, a new autoimmune mucocutaneous disease, paraneoplastic pemphigus (PNP), was described by Anhalt et al. The disease is characterized by distinctive clinical symptoms and signs, such as severe, painful mucosal erosions, polymorphous skin lesions, histopathologic hallmarks, and immunologic findings. The condition typically presents in patients with lymphoproliferative diseases, and primarily, malignancies. Castleman tumor is a distinct lymphoproliferative disorder of uncertain origin. To better understand PNP associated with Castleman tumor, and to explore a rational regimen to reduce the high mortality of this disorder and prevent its accompanying respiratory complications, we analyzed the characteristics of a group of patients in our hospital.

CLINICAL OBSERVATION AND TREATMENT

Patients' mucocutaneous lesions, results of routine blood tests, and systemic manifestations were investigated. A skin or mucosal biopsy specimen was taken to observe histologic features. If a patient presented with typical mucosal erosion (especially erosive stomatitis), typical histopathologic manifestations in skin or mucosa, and immunofluorescence changes, computed tomography (CT) of the chest, abdomen, and pelvis was carried out to search for
the underlying tumor. The tumors found were totally surgically removed. Histopathologic characteristics of the resected tumors were observed.

For the latest-diagnosed 6 patients who underwent surgery, 10 to 20 g of immunoglobulin (Ronsin Intravenous Immunoglobulin; Chengdu Rongsheng Pharmaceuticals, Chengdu, Sichuan, China) was given intravenously 1 hour before and during the operation. Among these 6 patients, preoperative treatment with 10 g of immunoglobulin daily for 3 days was given to 1 patient with severe lesions and respiratory symptoms. In 2 patients with bronchiolitis obliterans, 10 g of immunoglobulin every day or every other day for 3 to 6 days was given as a postoperative treatment.

**IMMUNOLOGIC FEATURES**

For indirect immunofluorescence, frozen sections of rat urinary bladder were used as the substrates, and the patients’ serum was used as the primary antibodies. Fluorescein isothiocyanate–conjugated anti–human IgG was the secondary antibody. After resection of the tumors, we also investigated the changes in autoantibody titers with indirect immunofluorescence.

**CULTURE OF TUMOR CELLS AND DETECTION OF AUTOANTIBODY FROM THE CULTURE MEDIUM**

Tumor cells were isolated after resection of the tumors and cultured as described previously. After the isolated tumor cells were washed 3 times with culture medium and cultured for more

Table 1. Characteristics of Mucocutaneous Manifestations and Tumors in 10 Patients in the Present Study

<table>
<thead>
<tr>
<th>Patient No./ Sex/Age, y</th>
<th>Duration of Illness, mo</th>
<th>Mucocutaneous Manifestations</th>
<th>Rash</th>
<th>Location of CD</th>
<th>Type of CD</th>
<th>BO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/39</td>
<td>4</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>LP</td>
<td>Ret</td>
</tr>
<tr>
<td>2/M/17</td>
<td>6</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>EM</td>
<td>Ret</td>
</tr>
<tr>
<td>3/M/30</td>
<td>5</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>PF</td>
<td>Ret</td>
</tr>
<tr>
<td>4/F/25</td>
<td>4</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>None</td>
<td>Med</td>
</tr>
<tr>
<td>5/M/29</td>
<td>7</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>PV</td>
<td>Ret</td>
</tr>
<tr>
<td>6/F/17</td>
<td>4</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>LP</td>
<td>Med</td>
</tr>
<tr>
<td>7/F/22</td>
<td>9</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>SJ</td>
<td>Ret</td>
</tr>
<tr>
<td>8/F/48</td>
<td>9</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>LP</td>
<td>Ret</td>
</tr>
<tr>
<td>9/F/41</td>
<td>8</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>LP</td>
<td>Ret</td>
</tr>
<tr>
<td>10/F/24</td>
<td>2</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>LP</td>
<td>Ret</td>
</tr>
</tbody>
</table>

Abbreviations: BO, bronchiolitis obliterans; CD, Castleman tumor/disease; EM, erythema multiforme; HV, hyaline vascular; LP, lichen planus; Med, mediastinum; NA, not available; PF, pemphigus foliaceus; PV, pemphigus vulgaris; Ret, retroperitoneum; SJ, Stevens-Johnson syndrome; +, present; −, absent.

Table 2. Clinical Findings in 18 Patients With Castleman Tumor From Previously Published Articles

<table>
<thead>
<tr>
<th>Source</th>
<th>Patient Sex/ Age, y</th>
<th>Mucocutaneous Manifestations</th>
<th>Rash</th>
<th>Location of CD</th>
<th>Type of CD</th>
<th>BO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tagami et al9</td>
<td>M/33</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>LP</td>
<td>Ret</td>
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<tr>
<td>Caporale et al10</td>
<td>F/21</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>(PV)</td>
<td>Med</td>
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<tr>
<td>Redon et al11</td>
<td>M/21</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>(LP)</td>
<td>Med</td>
</tr>
<tr>
<td>Ashinoff et al12</td>
<td>F/32</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>(LP)</td>
<td>Ret</td>
</tr>
<tr>
<td>Monpoint et al13</td>
<td>F/18</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>Plewig et al14</td>
<td>M/45</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>(LP)</td>
<td>Ret</td>
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<tr>
<td>Coulson et al15</td>
<td>F/15</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>(LP)</td>
<td>Ret</td>
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<tr>
<td>Fujimoto et al16</td>
<td>M/19</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>Ret</td>
<td>NA</td>
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<tr>
<td>Gill et al17</td>
<td>F/21</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>Med</td>
</tr>
<tr>
<td>Chin et al18</td>
<td>M/14</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Med</td>
<td>HV</td>
</tr>
<tr>
<td>Hsiao et al19</td>
<td>M/50</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>(LP)</td>
<td>Ret</td>
</tr>
<tr>
<td>Kim et al20</td>
<td>F/19</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>Ret</td>
</tr>
<tr>
<td>Saito et al21</td>
<td>F/20</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>NA</td>
<td>HV</td>
</tr>
<tr>
<td>Lemon et al22</td>
<td>M/13</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>(SJ)</td>
<td>Med</td>
</tr>
<tr>
<td>Hoffman et al23</td>
<td>M/52</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>Ret</td>
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<td>M/45</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>(LP)</td>
<td>Ret</td>
</tr>
<tr>
<td>Lee et al25</td>
<td>M/66</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>(LP, SJ)</td>
<td>Ret</td>
</tr>
<tr>
<td>Caneppele et al26</td>
<td>F/49</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>(LP)</td>
<td>Ret</td>
</tr>
</tbody>
</table>

Abbreviations: BO, bronchiolitis obliterans; CD, Castleman tumor/disease; EM, erythema multiforme; HV, hyaline vascular; LP, lichen planus; Med, mediastinum; NA, not available; PC, plasma cell; PV, pemphigus vulgaris; Ret, retroperitoneum; SJ, Stevens-Johnson syndrome; +, present; −, absent.
than 3 passages, the cell culture supernatant was collected, concentrated, and purified by means of centrifugal filters (Centrifcon Plus-50; Millipore Corp, Bedford, Mass). Positive serum from patients with PNP, uncultured medium, and supernatant from a culture of Namalwa cells, a cell line from human B-cell lymphoma, were used as positive and negative controls in the following tests.

Complementary DNA fragments coding linker regions of envoplakin (located at amino acids 1679-1812, GenBank U53786), periplakin (located at amino acids 1615-1755, GenBank NM002705), bullous pemphigoid antigen 1 (located at amino acids 1762-1891, GenBank M63618), and desmoplakin 1 (located at amino acids 1342-1482, GenBank J05211) were cloned and expressed as glutathione S-transferase fusion proteins. Glutathione S-transferase protein was used as the negative control, and the expressed fusion proteins were purified, separated, and transferred onto nitrocellulose membranes. We blotted the membrane strips with the concentrated cell culture supernatants.

RESULTS

The patients’ clinical data are shown in Table 1, and data from 18 patients in previously published reports are listed in Table 2.9-26 The clinical manifestations and the type and location of the associated tumors were similar in the 2 patient groups.

In 7 of the 10 cases, the white blood cell counts were high (12.5-16.7 × 10^9/μL) because of lung infection and inflammation in mucocutaneous lesions. Erythrocyte sedimentation rate was elevated in 7 cases and ranged from 25 to 77 mm in the first hour. The serum IgG level was elevated (1800-2140 mg/dL) in 3 cases. Three cases were found to have a positive antinuclear antibody in low titers.

CHARACTERISTICS OF MUCOCUTANEOUS AND RESPIRATORY MANIFESTATIONS

Mucosal Involvement

Oral lesions occurred in all 10 cases as the earliest complaint and presented as widespread blisters, erosions, ulcerations, and painful stomatitis affecting the entire oral cavity, tongue, and lips. Conjunctival erosions occurred in 8 of the 10 patients, and anogenital involvement occurred in 7 patients. Mucosal lesions may be the only sign, as they were in patient 4. The lesions in the mucosa were blisters, erosions, or ulcers, as well as erosive lichen planus–like lesions (Table 1, Figure 1).

Skin Lesions

Cutaneous lesions usually appeared after the onset of oral lesions and were polymorphic. Nine patients had rashes, including pemphigus-like in 2 cases, lichen planus-like in 5, and erythema multiforme-like in 1. Seven cases showed characteristic purple erythema on the fingers, palms, or soles (Figure 2).

Histopathologic Features of the Skin and Mucosal Lesions

Biopsy specimens were taken from cutaneous lesions in 9 cases and from oral mucosa in 5. Ten specimens showed acantholysis or blisters in the epidermis. Nine of them demonstrated suprabasilar acantholysis, and 1 showed acantholysis just below the granular layer. All of the specimens showed vacuolar interface changes with lymphohistiocytic infiltration in superficial dermis. In some cases extravasated red blood cells were found in papillary dermis. Necrotic keratinocytes, being a characteristic feature of the disease, were scattered in the epidermis of all of the examined specimens (Figure 3).

Symptoms of Respiratory System

Respiratory tract involvement or bronchiolitis obliterans was found in 7 of the 10 cases (Figure 4). Dry cough and dyspnea were the common symptoms. Four patients developed bronchiolitis obliterans several days after resection of Castleman tumors. Among them, 2 patients showed severe dyspnea with decreased PO2 (86.4-98.7 mm Hg). Patient 4 underwent a lung biopsy, which demonstrated dense lymphohistiocytic infiltration as well as fibrosis around bronchioles (Figure 4).

IMMUNOLOGIC FEATURES

In all of the 9 tested cases, indirect immunofluorescence disclosed a high titer of circulating IgG with intercellular staining of rat bladder epithelium (Figure 5). The titer ranged from 1:160 to 1:640 at the time of diagnosis. After resection of the Castleman tumors, the autoantibody titers decreased in most patients and became undetectable in 4 cases within 5 to 9 weeks.

On immunoblotting, IgG autoantibodies in serum from 9 patients recognized human keratinocyte proteins of 210 and 190 kDa, which were usually identified as the mem-

bers of the characterized antigens in PNP (Figure 5). Serum from some patients also recognized a 250-kDa protein band. However, positive bands of desmoplakin, desmoglein 3, and bullous pemphigoid antigen 1 were not detected by immunoblotting. This was probably due to the ineffective extraction of these antigens from the keratinocytes. Immunoprecipitation using radiolabeled keratinocyte extract may be a more sensitive method for the detection of antibodies against proteins of the plakin family.5

Of the 9 cases in which an enzyme-linked immunosorbent assay was performed, 6 had positive results, and in 2 cases results were weakly positive. One case had negative results.

LOCATION AND HISTOPATHOLOGIC FEATURES OF THE CASTLEMAN TUMORS

All patients remained asymptomatic and were diagnosed as having Castleman tumors after CT scanning. On CT scanning, 8 cases had tumors in the retroperitoneum and 2 in the mediastinum (Table 1). The diameters ranged from 3.0 to 12.0 cm. The tumors were usually globular or column-shaped, solitary masses with irregular margins. The average CT value of the masses ranged from 36 to 50 Hounsfield units, and they were usually isodense without necrosis or liquefaction. However, blotchy, striped, or branch-shaped calcifications could be seen in the center of the mass in 5 cases in this group; as calcification was found only in localized Castleman tumor, it was believed to be an important sign for the diagnosis of this tumor. All of the tumors were enhanced markedly and homogeneously after intravenous administration of contrast medium. The CT value increased to as high as 126 to 190 Hounsfield units, similar to that of great vessels in this circumstance.

The removed tumors were solid and measured 2 × 3 × 3 cm to 12 × 6 × 6 cm. Macroscopically, the tumors were solitary masses of various sizes with relatively intact and smooth capsules. The cut surface showed gray to yellow color and fleshy appearance. Histopathologically, the normal structure of the lymph node was effaced and replaced by numerous small follicular centers with prominent central vessels, which exhibited hyalinized walls and proliferative endothelial cells. The small follicular centers were surrounded by concentric layers of follicle center cells. The interfollicular areas showed vascular proliferation and variable numbers of plasma cells. Of the 10 cases, 9 tumors were hyaline vascular variants and 1 was a mixed variant (Figure 6).

Immunohistochemical staining showed that germinal centers in lymphoid follicles were dominated by...
B lymphocytes and CD34+ blood vessels located in the center of the follicles. The blood vessels were surrounded by concentric cuffs of B lymphocytes arranged in an onion-skin pattern, while the interfollicular areas were scattered with a few CD45Ro+ T lymphocytes (Figure 7).

COMMENT

FREQUENCY OF CASTLEMAN TUMOR

According to Anhalt et al, the most commonly associated neoplasm in PNP is non-Hodgkin lymphoma (42%). Others are chronic lymphocytic leukemia (29%), Castleman tumor (10%), thymoma (6%), retroperitoneal sarcomas (6%), and Waldenstrom macroglobulinemia (6%). However, in this series, 10 (77%) of 13 cases of PNP were found to be associated with Castleman tumor. In China, 14 cases of PNP were reported previously; 7 had a confirmed diagnosis of Castleman tumors, and 3 probably had Castleman tumors according to the manifestations and CT scans. Only 2 neoplasms were diagnosed as non-Hodgkin lymphoma, and 2 were other neoplasms. Therefore, 71% of the reported tumors associated with PNP were probably Castleman tumors. It seems that Castleman tumor is the most frequently encountered neoplasm associated with PNP in cases reported in China.

CASTLEMAN TUMOR AND ITS ROLE IN THE PATHOGENESIS OF PNP

The concentrated cultured media from 4 patients recognized recombinant linker regions of envoplakin, periplakin, desmoplakin 1, and bullous pemphigoid antigen 1 in the form of glutathione S-transferase fusion proteins, but did not recognize the 26-kDa glutathione S-transferase protein. Precultured medium and cultured medium from Namalwa cells showed no bands (Figure 8).

Castleman tumor represents lymphatic tissue proliferation of uncertain origin or is due to abnormal responses to various stimuli. Ashinoff et al postulated that possible expression of foreign tumor antigens that cross-react with epidermal antigens induce the autoreactive clones of T lymphocytes. Anhalt speculated that
tumors associated with PNP may produce plakin proteins that result in initiation of autoimmune responses. Other investigators believed that the autoimmune reaction was related to the epitope spreading.42,43

Our intensive clinical observation and laboratory investigation found that most of the patients’ lesions improved and that the titers of the circulation autoantibody decreased after resection of the tumors. We studied the role of B cells in the Castleman tumors in 7 cases. Results showed that clones of B lymphocytes in the Castleman tumor carrying similar specific rearranged immunoglobulin heavy-chain genes may have the structural basis for producing autoantibody in some of the cases.8 In one case, the cells isolated from the removed tumor were cultured, the cell culture medium was collected, and indirect immunofluorescence and immunoblotting were performed. Immunoglobulin G was found in the cell culture medium and can recognize the specific antigens in epithelia.8,44,45 Recently, rearranged immunoglobulin heavy- and light-chain variable region genes were cloned and their sequences were analyzed in Castleman tumors associated with PNP. A high incidence of somatic mutations in complementarity-determining regions and framework regions was observed in the cloned variable region of heavy-chain and light-chain genes. These clones were found to have experienced switch recombination and have the structural basis to produce autoantibodies.46,47 In this series of patients, IgG antibodies in the cell culture media were found to recognize the recombinant envoplakin, periplakin, and desmoplakin fusion proteins, which are believed to be the specific target antigens of PNP. Therefore, we believe that the autoantibodies are directly produced by the cells in the Castleman tumor. Because the autoantibodies originated from the Castleman tumor, the early detection and removal of the tumor is essential for the treatment of this tumor-associated autoimmune syndrome.

**USE OF INTRAVENOUS IMMUNOGLOBULIN IN PREVENTION OF BRONCHIOLITIS OBLITERANS**

Bronchiolitis obliterans is frequently found in PNP and may cause respiratory failure and death.2,18,21,23 A previous study21 showed that the autoantibodies could be deposited in bronchial epithelia and that the affected bronchioles developed severe luminal stenosis (up to 80%-90%). Therefore, autoantibody-mediated injury takes an important role in the pathogenesis of bronchiolitis obliterans, although infections and toxic effects induced by chemotherapy and neoplasm may also cause pulmonary injury.23,48,49 Nikolskaya et al27 reported that 22 of 28 patients with Castleman tumor in association with PNP died, most of them of bronchiolitis obliterans.
Intravenous administration of immunoglobulin has been widely used in the treatment of autoimmune diseases such as pemphigus, bullous pemphigoid, and systemic lupus erythematosus. The possible mechanism depends on the interaction of the Fc portion of immunoglobulin with Fc receptors and on the modulation of the activation and effect functions of B lymphocytes. Intravenous administration of immunoglobulin also neutralizes pathogenic autoantibody and has a strong anti-inflammatory effect depending on its interactions with the complement system, cytokines, and endothelial cells. However, few articles have been published about the effect of intravenous administration of immunoglobulin in the treatment of PNP.51,53

In our study, the first 4 of the 10 patients did not accept intravenous administration of immunoglobulin, and 3 of them developed severe bronchiolitis obliterans within 1 week after the operation. However, in the other 6 patients, respiratory symptoms were controlled or prevented by giving immunoglobulin intravenously before and during the operation. The response to the intravenous administration of immunoglobulin usually started within 3 days. One patient who started immunoglobulin treatment before surgery showed improvement of the skin lesions and bronchiolitis obliterans within 1 week. However, intravenous administration of immunoglobulin alone cannot substitute for surgical treatment and cure the PNP. Recently, a recurrent Castleman tumor was found in the abdomen of a 32-year-old patient (patient 3 in Table 1) when his skin lesions relapsed 2 years after the surgery. The cutaneous blisters were under control again after the second surgical removal of the tumor. Unfortunately, his disease relapsed again. Intravenous administration of immunoglobulin can temporarily control the skin lesions, but the patient's condition worsened when he did not have the recurrent tumor removed again. Therefore, we believe that both early removal of the Castleman tumor and intravenous administration of immunoglobulin are important to prevent the development of severe bronchiolitis obliterans.

SURGICAL REMOVAL OF THE TUMOR AND PROGNOSIS

All of the observed patients showed poor response to treatments such as corticosteroids, immunosuppressive drugs, and chemotherapeutic drugs before removal of the tumor. However, after total resection of the tumors, 7 of the 10 patients responded well to general dermatologic management. Cutaneous lesions disappeared or improved within 6 to 11 weeks, and mucosal lesions significantly improved within 5 to 10 months. Serum autoantibody levels decreased in 6 to 8 weeks. Gili et al17 reviewed 5 cases of PNP associated with Castleman tumor, and lesions in all cases improved after surgical removal of the tumors. Jansen et al24 also reviewed 12 cases of similar disease, and 8 of the 12 patients markedly improved after removal of Castleman tumors. Early removal of the Castleman tumor has proved to be the most important management for the disease. If Castleman tumor is detected, total resection of the tumor is the only way to achieve complete resolution of the disease. As we have stated, intravenous administration of immunoglobulin is recommended before and during the operation. During the operation it is important to block the blood supply to the tumor as soon as possible and avoid squeezing the tumor. Total resection including the connective tissue envelope is crucial for a good prognosis. Large tumors tend to recur. Early detection and resection are essential for the treatment of the disease.

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Critical revision of the manuscript for important intellectual content: Zhu, R. Li, and Tu. Administrative, technical, and material support: J. Wang, Tu, R. Wang, Zhang, T. Li, Chen, A. Wang, S. Yang, Wu, H. Yang, and Ji. Study supervision: Zhu and R. Li.

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REFERENCES


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