Infection and Drug Resistance

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CASE REPORT

Clinical Diagnostic Challenge in a Case of Disseminated *Talaromyces marneffei* Infection Misdiagnosed Initially as Pulmonary Tuberculosis: A Case Report and Literature Review

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Abstract: This case reports a middle-aged male patient who was HIV-negative and initially misdiagnosed as pulmonary tuberculosis but was eventually diagnosed with disseminated *Talaromyces marneffei (T. marneffei)* infection by next-generation sequencing. The patient presented with respiratory symptoms, recurrent bone pain, and subcutaneous masses as the main symptoms. After one year of antifungal treatment, the symptoms improved obviously, but the symptoms recurred after two weeks of drug withdrawal, and the symptoms were relieved after re-administration of antifungal drugs again. This report highlights the need for the rapid evaluation of fungal infections with metagenomic next-generation sequencing (mNGS) in patients with an inadequate diagnostic basis for tuberculosis infection or a poor response to antituberculosis drugs. In addition, long-term follow-up is needed to observe disease recurrence in patients with disseminated *T. marneffei* infection.

Keywords: *Talaromyces marneffei*, HIV-negative patient, tuberculosis, misdiagnose, Next-generation sequencing

Introduction

Talaromycosis, caused by *T. marneffei* infection, is a severe fungal disease that primarily occurs in Southeast Asia, including Thailand, Vietnam, and China. It is the third most common opportunistic infection in these three countries. In China, the majority of cases have been reported in Guangdong and Guangxi provinces.[1] The disease primarily affects individuals with compromised immune systems owing to conditions such as Acquired Immune Deficiency Syndrome (AIDS), cancer treatments, and organ transplants. While AIDS patients are particularly vulnerable, there has been a notable increase in *T. marneffei* infections among both immunocompromised and non-immunocompromised individuals without HIV in recent years.[2,3] Despite being recognized as the second most feared fungal infection globally in 2018, there is a lack of global attention towards the diagnosis and treatment of talaromycosis.[4] The clinical manifestations of *T. marneffei* infection are often not easily distinguished from other pathogenic infections due to the complex and diverse clinical symptoms and lack of specificity in laboratory and imaging studies, which often lead to misdiagnosis of tuberculosis, non-tuberculous mycobacterium infection, bacterial pneumonia, or multiple myeloma. Tuberculosis is the most commonly misdiagnosed condition, with approximately 80% of *T. marneffei* cases initially mistaken for tuberculosis.[5]

Although there have been previous studies on the clinical diagnosis and treatment of *T. marneffei* infection, there have been no detailed case descriptions of its misdiagnosis as tuberculosis. The aim of this article is to present a case report of disseminated *T. marneffei* infection initially misdiagnosed as pulmonary tuberculosis and provide a brief overview of

Received: 4 May 2024
Accepted: 19 August 2024
Published: 29 August 2024

relevant literature. Our findings may help to improve the clinician's awareness of the diagnosis of *T. marneffei* infection in HIV-negative patients, especially in the state of autoimmune disease, even if the lymphocyte count is normal, the possibility of specific fungal infection should be considered.

Case Presentation

A 43-year-old male was admitted to our hospital with recurrent cough and sputum for 1 year, along with joint pain in all extremities for 10 months. Approximately a year ago, the patient experienced symptoms of cough, sputum production, and fever, which led to hospitalization at a local hospital. During hospitalization, the interferon-gamma test of this patient was negative, and the Mantoux test had not been performed. The patient was diagnosed with pericardial and pleural effusions. The fluid obtained through the puncture was thick and brown in color. After ruling out tumors and common pathogenic infections, the initial hospital considered a clinical diagnosis of pulmonary tuberculosis and administered anti-tuberculosis treatment. However, the patient's symptoms were not well relieved. The patient developed a mass on the head three months prior to admission. He was admitted to another hospital for 20 days and was diagnosed with pulmonary fungal infection and ankylosing spondylitis. During his treatment, he received hydroxychloroquine, voriconazole, piperacillin, and tazobactam, which resulted in disappearance of the mass. Approximately one month ago, the patient had developed masses in the head, neck, axilla, arms, and abdomen. The arm mass had ruptured, and yellow-white pus was observed to flow out. It is worth noting that four years ago, the patient had resided in Myanmar for an extended period and worked as a driver. In addition, he had a history of bamboo rat consumption.

Physical examination revealed two masses measuring 4×5 cm on the neck (Figure 1A and C), a mass measuring 4×3 cm on the left axilla, and three masses measuring 1×1 cm on the right upper arm that were firm to touch (Figure 1B). There were a few moist rales in both lungs.

Laboratory results revealed white blood cell count of 41.23×10^9/L, neutrophil percentage 88.4%, hemoglobin 89g/L; C-reactive protein 129.4 mg/L; procalcitonin 6.92ng/mL; total bilirubin 43.3umol/L, direct bilirubin 30.5umol/L, indirect bilirubin 12.8umol/L, albumin 13.9g/L, globulin 54.1g/L; CD4+T cell count of 1730 cells/μL and CD8+T cell count of 1325 cells/μL; HIV antibody negative; interferon-gamma test negative; parasite antibodies negative; autoimmune antibodies negative; direct anti-human globulin test positive, indirect anti-human globulin test negative; positive for HLA-B27.

Chest computed tomography (CT) revealed scattered spots, nodules, and strip shadows in both lungs with uneven density and blurred edges, multiple enlarged lymph nodes in mediastinum and bilateral axilla. Local bone destruction and swelling of the surrounding soft tissues were observed in the left 4th rib, and a flake-like slightly low-density shadow was

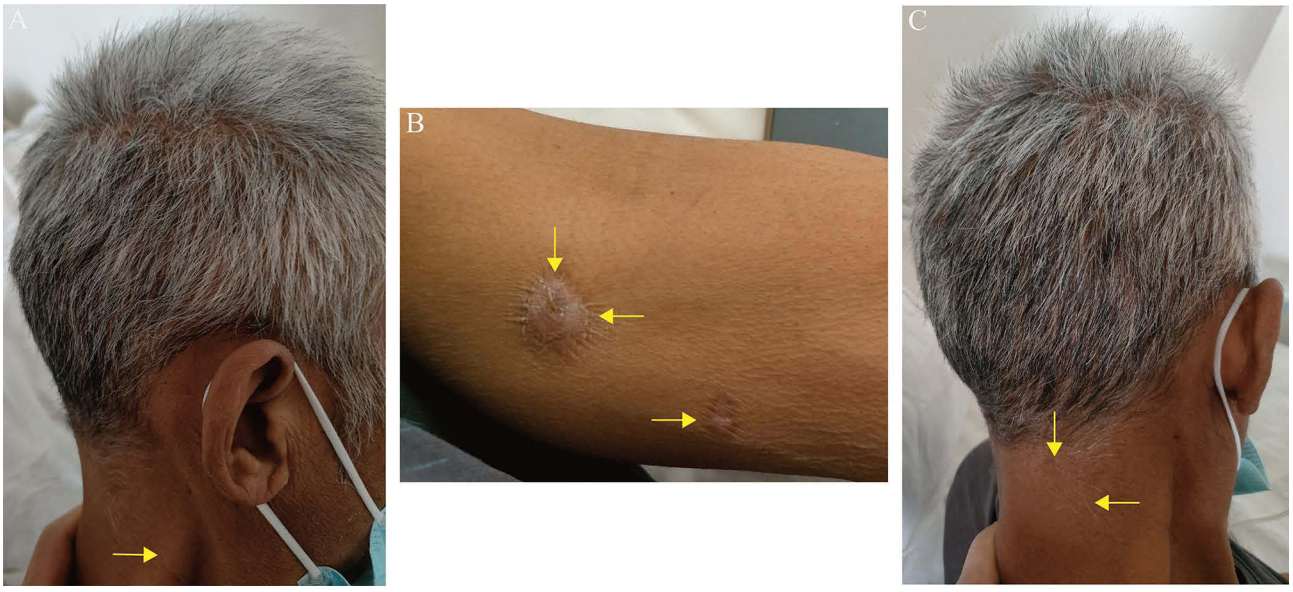

Figure 1 (**A–C**) yellow arrows indicate patient's skin masses in the right neck, right upper arm, and back neck, some of which were crusted.

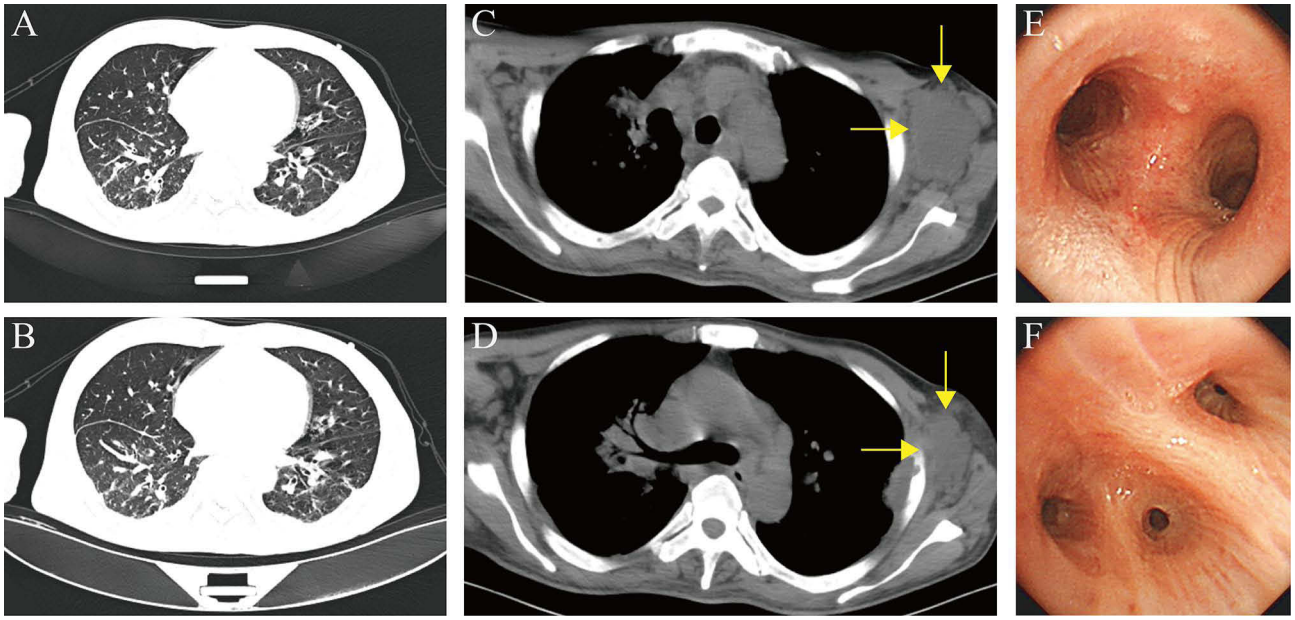

Figure 2 (**A–F**) Chest CT and bronchoscope. A and B indicate infectious lesions in both lungs. (**C** and **D**) yellow arrows show local bone destruction in the left 4th rib and flaky axillary low-density shadows. (**E** and **F**) show chronic inflammatory changes in the bilateral bronchus with mild stenosis of some lumens, tubercles, and right middle lobe mucous tubercles.

observed. The largest layer was located in the axilla, with a range of 7.6×4.7 cm (Figure 2A–D). CT tomography of the hip joint showed fluid accumulation and local bone erosion in both hip joints. Bronchoscopy showed no special features, only chronic inflammatory changes (Figure 2E and F).

Magnetic resonance imaging (MRI) revealed slightly longer and patchy T2 and T1 signals in the thoracic vertebrae, lumbar vertebrae, sacrum, and bilateral iliac bones. The lesions showed slightly high signal intensity on T2 fat suppression and were significantly enhanced by enhanced scan, suggesting that the possibility of infectious lesions was high. An abscess formed around the right sacroiliac joint and bilateral hip joints (Figure 3A–D).

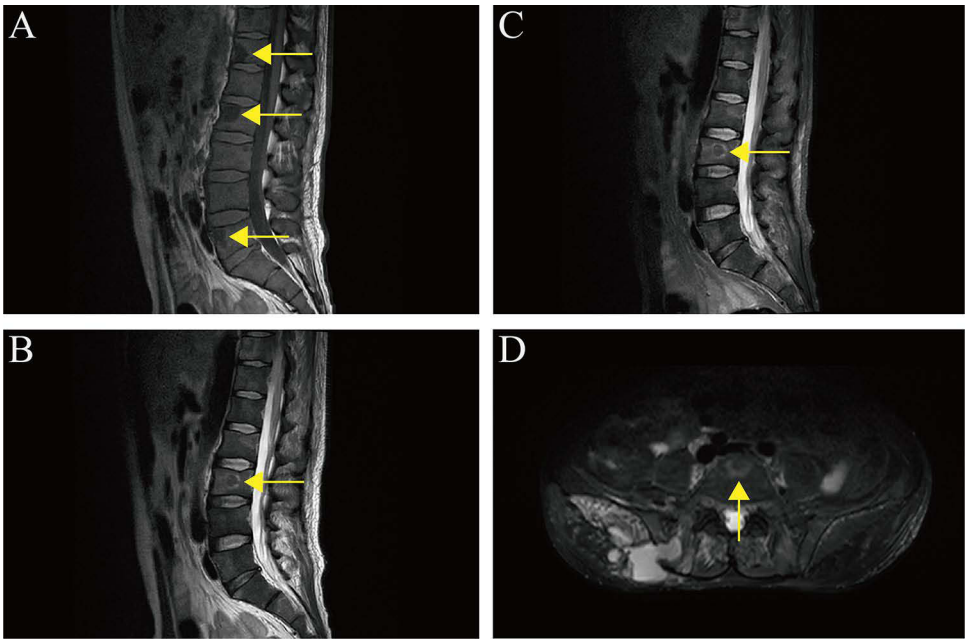

Figure 3 (**A–D**) Spinal MRI yellow arrows indicate abnormal signals in the thoracic vertebrae, lumbar vertebrae, sacrum and bilateral ilium, and abscess formation around the sacroiliac joint.

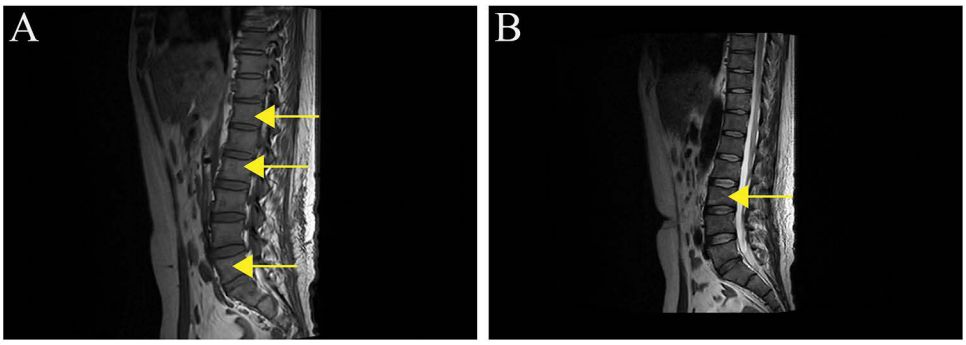

Figure 4 (**A** and **B**) Spinal MRI yellow arrows indicate that abnormal signals of the thoracic and lumbar vertebrae are significantly reduced compared with (Figure 3A and B).

The patient was referred to our hospital with an initial diagnosis of invasive pulmonary tuberculosis combined with gram-negative bacterial infection. Antituberculous drugs were continued, and intravenous meropenem was administered. However, after 4 days, there was no improvement. At this time, the bone marrow aspiration smear suggested infectious anemia and the Aspergillus galactomannan test was positive. Therefore, we considered the possibility of fungal infection. After intravenous fluconazole administration, the patient's fever and pain were relieved.

A lymph node biopsy was performed to obtain an accurate diagnosis, and pathological examination revealed few lymphocytes but no evidence of a tumor or tuberculosis. Results of bronchoalveolar-lavage fluid testing for Mycobacterium tuberculosis DNA and Xpert were negative. Additionally, a previous culture of the bone marrow fluid showed the presence of fungal hyphae, although the specific type of fungus was not identified. Culture of the subcutaneous abscess puncture showed no bacterial growth and no C*andida* growth. Subsequently, pus from the skin mass was aspirated for mNGS, which confirmed the *T. marneffei* infection.

Following the final diagnosis of *T. marneffei* infection, fluconazole was substituted with intravenous voriconazole in accordance with the treatment protocol for the disease. Oral itraconazole therapy was continued after discharge. We followed the patient, after one year of antifungal treatment, the symptoms improved obviously, the pulmonary symptoms were basically relieved, the skin mass disappeared, the bone pain was relieved, and MRI showed that the bone destruction was improved (Figure 4A and B compare with Figure 3A and B). However, the swelling and pain of the lower leg occurred two weeks after drug self-withdrawal. Upon re-administration of antifungal drugs, the symptoms improved again.

Discussion

T. marneffei infection is more common in HIV-infected individuals. In China, epidemiological research indicates that 87.72% of individuals infected with *T. marneffei* are HIV-positive. However, in recent years, the incidence of HIV-negative patients has gradually increased. Bamboo rats and humans are the main animal hosts of *T. marneffei*.[6] It is currently generally accepted that the inhalation of airborne conidia by humans from their surroundings (such as soil), which then spread to other parts of the body, is the main pathogenic route.[7] Therefore, a history of residing or traveling in an endemic area and exposure to environments where bamboo rats live may well serve as an important clue for a physician to diagnose *T. marneffei*.[8] This patient had eaten bamboo rats many years ago, but since he was non-HIV, his condition was not taken seriously. It should be noted that *T. marneffei* infection can occur in individuals with normal immune function, although it is considered to be extremely rare.[9] Most people infected with *T. marneffei* develop their first symptoms within 6–12 months of leaving endemic areas, but there is evidence that the incubation period can be up to 10 years.[10] To ensure timely diagnosis and treatment, it is crucial to obtain a comprehensive travel history and consider the possibility of uncommon pathogen infections in patients presenting with specific infections.

The clinical features of talaromycosis are complex and difficult to identify. Common clinical manifestations of talaromycosis include fever, weight loss, anemia, lymphadenopathy, hepatosplenomegaly, respiratory signs, and skin lesions, which may be easily mistaken for symptoms of other infectious diseases, especially tuberculosis. Both *T. marneffei* infection and tuberculosis can induce fever, coughing, sputum production, and bone deterioration. Owing

to the limited success of smear staining microscopy in clinical samples as well as the extended culture duration, no single test can definitively confirm all cases of tuberculosis.[11] Therefore, a comprehensive approach involving clinical evaluation, imaging, smear tests, tuberculosis cultures, molecular techniques, histological results, and treatment strategies is necessary. In HIV-infected patients, *T. marneffei* tends to spread to multiple organs. In non-HIV-infected patients, the infection may be localized or disseminated depending on the underlying immunocompromising condition and timing of diagnosis. In terms of clinical characteristics, individuals without HIV infection are more predisposed to developing bone and joint infections.[5] In HIV-negative patients, there is a significant increase in white blood cell, neutrophil, and lymphocyte counts. Furthermore, chest imaging of *T. marneffei* infection lacks specificity, and chest CT scans often show a variety of lung abnormalities similar to pulmonary tuberculosis, including infiltration, nodules, cavities, ground-glass shadows, diffuse miliary shadows, and pleural effusions.[12]

The main symptoms of this patient were lung infection in the early stage of the disease, and the typical clinical features of HIV-negative infected individuals, such as multiple skin abscesses and osteolytic lesions, appeared during the course of the disease. However, lung CT lacks specificity, making it challenging to distinguish between these features and tuberculosis infection. Despite receiving medication for up to six months, the patient did not show any response. The main reasons for misdiagnosis are insufficient understanding of *T. marneffei* infection and the complicated and diverse clinical symptoms of patients, which makes it easy for doctors to consider multiple causes in diagnosis. The patient also had ankylosing spondylitis and autoimmune hemolysis. The manifestations of these autoimmune diseases have increased the confusion regarding diagnosis. In addition, owing to the combination of multiple drugs, it was difficult to determine the actual cause, and it was easy to mistake anti-tuberculosis drugs to play a key role. In addition to the atypical clinical features, the low percentage of *T. marneffei* infections in HIV-negative patients often results in the pathogen being overlooked during clinical diagnosis.[13]

Invasive fungal infections are more prevalent in patients with weakened immune systems. Traditionally, most individuals diagnosed with talaromycosis are HIV-positive. However, in recent years, there has been an increase in the number of *T. marneffei* infections among HIV-negative patients with primary or secondary immunodeficiency. Primary immunodeficient patients with anti-interferon gamma (Anti-IFN-g) autoantibodies (auto-Abs) and secondary immunosuppressed patients who received novel therapies, such as anti-CD20 monoclonal antibodies (MAbs) or kinase inhibitors, have shown a higher incidence of talaromycosis.[14,15] Anti-IFN-g autoantibody (AIGA) syndrome, first reported in 2004, is an emerging adult-onset immunodeficiency syndrome characterized by the presence of high levels of anti-IFN-G autoantibodies in patients.[16] These patients are susceptible to infection by intracellular pathogens, studies have shown that 20.41% of HIV-negative adult patients with *T. marneffei* infection were AIGA-positive.[17] This antibody can significantly suppress the immune response of CD4+ T cells, and these patients are susceptible to infection by intracellular pathogens. Even if the lymphocyte count is normal, activation and proliferation of CD4+ T cells are impaired. In a 2020 study, 15 HIV-negative patients with *T. marneffei* infection were compared to 18 healthy controls. The results of cell function test indicated that the activation and proliferation of CD4+ T cells, cytotoxic ability of CD8+ T cells and NK cells, and cytokine secretion ability of CD4+ T cells and NK cells were decreased when compared to healthy controls. Therefore, *T. marneffei* infection may be regarded as an indicator of immunosuppression.[18] Although this patient was HIV negative and the count of CD4+T lymphocytes and CD8+T lymphocytes in the lymphocyte subsets did not decrease, indicating autoimmune dysfunction due to autoimmune diseases such as ankylosing spondylitis and autoimmune hemolysis. We should clarify whether there is immune deficiency. If conditions permit, Anti-IFN-g autoantibodies (AIGA) and lymphocyte function can be detected to further clarify pathogenesis.

T. marneffei mycological culture is the gold standard for clinical identification of pathogenic bacteria. However, due to the long culture time, low positive rate, and lack of specificity in the early stage of the disease, there is a high rate of missed diagnoses, which leads to a delay in clinical antifungal therapy. In some cases, the fungus is difficult to grow and no commercial serological test is available.[19] As an advanced detection method, mNGS can rapidly and accurately identify pathogens. The accuracy and timeliness of mNGS are crucial in diagnosing complex and challenging infections. Early diagnosis and treatment of *T. marneffei* infection are key to improve prognosis, and the diagnostic value of mNGS can be increasingly emphasized in different clinical application scenarios.

Some questions remain in this case, in our clinical work, when dealing with patients with complex infections, we should conduct multi-site sampling and testing to observe the detection rate of different types of specimens, and also provide valuable data for diagnosing HIV-negative patients with disseminated *T. marneffei* infection. In addition, this patient had disease recurrence after drug self-withdrawal. Despite the patient's response to medication resumption, the final prognosis is unclear.

Conclusion

Clinical implications of the paper as this is a rare report referring to disseminated *T. marneffei* misdiagnosed as tuberculosis. It aims to raise awareness among clinicians regarding the possibility of *T. marneffei* infection in non-endemic areas and HIV-negative patients, and to pay attention to the application value of mNGS in infected patients with diverse clinical manifestations. More importantly, it also highlights the need for the rapid evaluation of fungal infections with metagenomic next-generation sequencing (mNGS) in patients with an inadequate diagnostic basis for tuberculosis infection or a poor response to antituberculosis drugs. In addition, long-term follow-up is needed to observe disease recurrence in patients with disseminated *T. marneffei* infection.

Ethics Approval and Consent to Participate

Ethical approval was not required for this case report in accordance with the local guidelines. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Consent for Publication

Written informed consent was obtained from the patient's family for the publication of this case report.

Acknowledgments

We would like to acknowledge the reviewers for their helpful comments on this paper.

Funding

This research was financially supported by Prince of Songkla University and Ministry of Higher Education, Science, Research and Innovation under the Reinventing University Project (Grant Number REV65022).

Disclosure

Jingyi Dai is an international research fellow in the Department of Epidemiology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla, Thailand. The authors declare that they have no competing interests in this work.

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