To the Editor: In September of 2016, a 26-year-old farmer from Yunnan Province with no medical or drug history exhibited painless cutaneous nodules on his chest. Later the nodules gradually appeared on his limbs, face, and trunk. After half a month, he had moderate to high-grade fever (39.5°C) and numbness of limbs. He reported no coughing, diarrhea, arthralgia, and myalgia. There was no similar illness in his family. Laboratory tests in a local hospital showed elevated white blood cell and neutrophil count. Serology tests for infection were negative. Anti-neutrophil cytoplasmatic antibodies (ANCA) and myeloperoxidase ANCA (MPO-ANCA) were positive. The computed tomography of chest was normal. Based on the clinical and laboratory manifestations, he was diagnosed as ANCA-associated vasculitis (AAV) and was initially treated with intravenous methylprednisolone 80 mg/day and cyclophosphamide (0.4 g/2 weeks) for four times in the local hospital. In the course of the treatment, fever and skin nodules were temporarily relieved, but the peripheral nerve damage did not worsen and the skin nodules and numbness of limbs ultimately revealed. The patient was admitted to the center for disease control and prevention for multi-drug therapy. In the 7 months follow-up with the patient, the skin nodules and fever were resolved, but the peripheral nerve damage did not achieve disease remission.

In 2007, the number of new leprosy cases reported was 258,133 and in 2016, the number of reported cases had slowly declined to a total of 214,783 worldwide, including 677 in China,11 which means leprosy is still a public health problem. China’s leprosy burden is disproportionally affecting the country, with the confirmed cases mainly occurring in high-epidemic provinces such as Yunnan, Guizhou, Sichuan, and Guangdong. Some patients do not seek treatment or might conceal contact history because of the social stigmatization and discrimination towards the disease. Thus, they become the “invisible” disease origin. If stigma and discrimination are not addressed, leprosy will most likely persist. The patient in this case denied previous contact with any leprosy patients. We believe this was probably because he lacked knowledge towards leprosy so that he might have neglected former contact history.
Leprosy is a heterogeneous disease. Its early symptoms and clinical signs including nerve damage and skin morphology are not always specific, so the diagnosis may sometimes be quite difficult and result in diagnostic pitfalls. A study of misdiagnoses of leprosy during the year 1989 to 2011 in China showed it took an average of 3.9 years before patients were given the correct diagnosis (76.0% were multi-bacillary leprosy), with the longest duration was 23 years. The correct diagnosis was difficult to make in our case because of the two following reasons: the clinical symptoms between AAV and leprosy reaction were similar, such as high-grade fever, skin nodules, and sensory loss, and the diagnosis of leprosy was complicated by the presence of MPO-ANCA.

The diagnosis of AAV remains a challenge for rheumatologists. The clinical spectrum of AAV is broad and the presentation can be quite varied, ranging from a skin rash to multisystem involvement. In 1990, the American College of Rheumatology published criteria for the classification of seven types of systemic vasculitis, but there were important limitations. Microscopic polyangiitis (MPA) was not included and the criteria were developed before the widespread use of testing for ANCA. After two decades, there were still no accepted criteria for the diagnosis of MPA, thus the diagnosis was still based on clinical manifestations, immunology tests, and biopsy. In 2017, the American College of Rheumatology proposed a provisional hierarchically clustered and weighted classification criteria for AAV: MPA classification requires a score of 5 or more, and the presence of MPO-ANCA alone required 6 points. The patient in this case fulfilled the classification criteria of MPA, but the real cause of his disease turned out to be leprosy infection, which illustrated that the validity, sensitivity, and specificity of the provisional criteria for AAV still need to be tested and improved in clinical practice.

The presence of autoantibodies is an important characteristic in “leprosy mimicking vasculitis” cases. The most frequently demonstrated autoantibodies in leprosy are rheumatoid factor, anti-nuclear antibody, anti-Sjogren syndrome B antibody, ANCA, and anti-phospholipid antibodies. There are some plausible theories explaining the presence of serological autoantibodies in leprosy. *M. leprae* infects hosts through mucosa of upper respiratory tract and then binds to G domain in Schwann cells. Schwann cells can then process and present the antigen to antigen-specific T lymphocytes and trigger the immune responses. Molecular mimicry and polyclonal B-cell activation can also contribute to autoantibody production. The antigen-antibody complex deposits on the blood vessel wall, leading to inflammation and multisystem damages. Moreover, an integrative analysis of leprosy susceptibility genes indicated a common autoimmune profile, and found the genes were enriched in activation and regulation of immune responses.

Clinicians need to be aware of leprosy when patients have neurologic, dermatologic, or rheumatic symptoms. The possibility of underlying infectious disease in patients with manifestations of vasculitis should always be considered. Skin biopsy is especially necessary in patients who appear to have autoimmune disease with atypical skin lesions.

**Declaration of patient consent**

The authors certify that they have obtained appropriate patient consent form. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initial will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.
Conflicts of interest

None.

References

1. Global Leprosy Update, 2016: Accelerating Reduction of Disease Burden. WHO Weekly Epidemiological Record, 2017. Available from: http://www.who.int/wer. [Accessed May 14, 2020]
2. Zheng DC, Chen WJ, Wang XH, Chen YF. Retrieval and analysis of literatures on misdiagnosis of leprosy during the years 1989-2011 (in Chinese). Diagn Ther J Dermatol-Venereol 2012;19:285–287. doi: 10.3969/j.issn.1674-8468.2012.05.007.
3. Seeliger B, Sznajd J, Robson JC, Judge A, Craven A, Grayson PC, et al. Are the 1990 American College of Rheumatology vasculitis classification criteria still valid? Rheumatology (Oxford) 2017;56:1154–1161. doi: 10.1093/rheumatology/kex075.
4. El-Gendy H, El-Gohary RM, Shohdy KS, Raqab G. Leprosy masquerading as systemic rheumatic diseases. J Clin Rheumatol 2016;22:264–271. doi: 10.1097/RHU.0000000000000379.
5. Singh J, Yadav AR, Mohanty KK, Katoh K, Boht D, Sharma P, et al. Molecular mimicry between HSP 65 of Mycobacterium leprae and cytokeratin 10 of the host keratin; role in pathogenesis of leprosy. Cell Immunol 2012;278:63–75. doi: 10.1016/j.cellimm.2012.06.011.

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