# Recurrent fever and cutaneous nodules: leprosy masquerading as anti-neutrophil cytoplasmic antibodies associated vasculitis

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*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 cytoplasmic 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 reoccurred when prednisone tapered to 20 to 30 mg/day. The recurrent fever, skin nodules, and numbness of limbs had lasted for 2 years, and thus, he was referred to the Sichuan University West China Hospital.

Upon physical examination in our hospital, the patient had both firm and soft textured discrete red nodules measuring 0.5 to 1.0 cm on his face, limbs, and trunk [Figure 1]. There were a few enlarged lymph nodes ranged from 0.5 to 1.0 cm in diameter around his neck, armpit, and inguinal region; neurological examination revealed decreased superficial sensation in both forearms and right lower limb. Laboratory tests showed increased white blood cell count ($23.63 \times 10^9$/L) and raised neutrophil percentage (84.7%). The plasma level of procalcitonin was 0.07 ng/mL, erythrocyte sedimentation rate was 43 mm/h, and C-reactive protein was 164 mg/L. Urinary sediment microscopy test was normal. Immunology test result showed positive ANCA and MPO-ANCA. The imaging results of head, chest, and abdomen were normal. Electroneuromyography test illustrated right common peroneal nerve and bilateral ulnar nerve damage. The smear of light yellow viscous liquid from the ulcerated skin nodule revealed abundant acid-fast bacilli. The inguinal lymph node biopsy revealed non-caseating granulomatous inflammation and an infiltrate of neutrophils and lymphocytes in dermis. Polymerase chain reaction confirmed *Mycobacterium leprae* infection. We diagnosed him with multi-bacillary leprosy with type II leprae reaction. It was not until 2 years later that the truth behind the recurrent fever, skin nodules, and numbness of limbs was 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,[1] 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.[2] 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.

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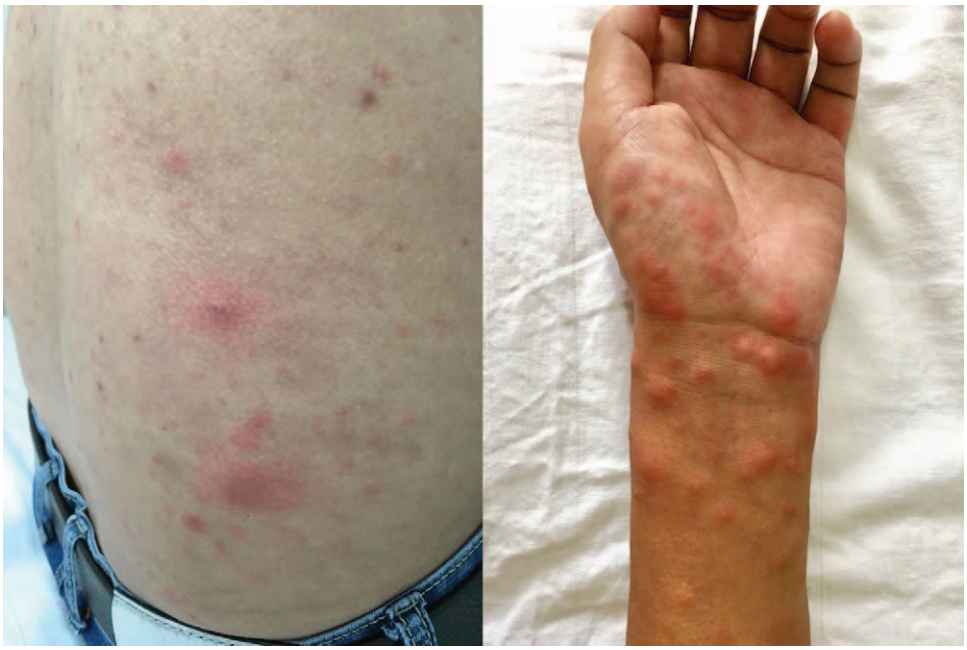

**Figure 1:** Discrete red nodules on the patient's trunk and forearm.

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.[2] 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.[3] 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, ANCAs, and anti-phospholipid antibodies.[4] 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.[5] 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, Ragab G. Leprosy masquerading as systemic rheumatic diseases. J Clin Rheumatol 2016;22:264–271. doi: 10.1097/RHU.0000000000000379.
5. Singh I, Yadav AR, Mohanty KK, Katoch K, Bisht 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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