Behcet's disease: a case report with cerebral artery infarction caused by cerebral arteritis as the first symptom only with elevated Interleukin-8(IL-8)

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Case report

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Abstract

Background Behcet's disease (BD) is a multi-systemic vasculitis which generally characterized by oral and genital ulcers as well as ocular and skin lesions. There are only 5% of BD patients get neurological involvement and it usually occurs 4-6 years later after the initial symptoms. Early onset of neurological impairment symptoms makes it difficult to diagnose and treat definitely. Case presentation A 38-year-old man with BD was referred to our hospital due to a sudden numbness and weakness in his left extremities. Brain magnetic resonance imagine (MRI) showed acute cerebral infarction. The symptom was recurred in several months and then there were skin rash, oral ulcer and arthrodynia. High resolution MRI of brain suggested cerebral artery intima thickening. Laboratory examination showed the increase of IL-8. Biopsy of the skin rash showed small vessel vasculitis. We treated the patient with an immunosuppressive agent mycophenolate mofetil (MMF), hydroxychloroquine and colchicine. Now, patients still insist on taking immunosuppressive agents, all symptoms were alleviated after treatment, rash decreased in the past six months, no acute stroke, no recurrence of oral ulcer. Conclusion This case demonstrates that neurological involvement might be the first symptom of Behcet's disease, and IL-8 could be a useful marker for diagnosis.

Background

Behcet's disease (BD) was firstly reported by the Turkish doctor Behcet in 1937. It is an agnogenic and multi-systemic disease based on small vessel vasculitis. The typical clinical performance is eye-mouth-genital triad, which means recurrent oral ulcer, ocular uveitis and genital ulcer[1].The condition of this disease recurred but most patients have a good prognosis.

The etiology and pathogenesis are still unclear. Generally it is believed that it may due to genetic, immune factors or pathogen infections. Immune factors play an important role in the pathogenesis of BD Cytokines, such as IL-1, IL-8, TNF-α, heat shock proteins, macrophages activation and autoimmune factors, etc. are all participated in the onset[2-4].

BD is mainly distributed along the historical Silk Road[5]. Recent years, coutries where there were none BD reported or rarely cases. In the existing literature, Turkey has the highest incidence (20-240 patients in 100,000 people)[6, 7]. The incidence in China is 14 patients in 100,000 people[8]. Europe has low incidence[9, 10].

The diagnosis of BD currently relies only on clinical symptoms, we used to use the ISG diagnostic criteria developed in 1990.[11] In 2012, international teams from 27 countries submitted data based on 2556 BD cases and 1163 BD-like cases or cases with at least one of the major BD symptoms to adjust the international criteria for BD□ICBD□. This criteria improved the sensitivity and specificity of BD diagnosis greatly, allowing patients to get early diagnosis and timely treatment, and obtain a good prognosis[12].

BD is classified into vascular type, neurological type, gastrointestinal type, etc. according to the damage of its visceral systems. The first BD case with nervous system involvement was reported by Knapp in

1941[13]. Then Cavara and D'Ermo proposed a widely accepted term "neuro-Behcet's disease" for this type[14]. Patients with nervous system involvement of BD have been reported to account for 3.2%-49%, mostly about 5%[15, 16]. Nervous system symptoms mostly occur 4-6 years after the onset of BD[14]. But some of the patients have neurological symptoms at the same time with or before the classical symptoms, which may lead to diagnostic confusion, and these patients might be more than reported[17].

The pathological feature is various types of arteriovenous vasculitis which mainly affect small vessels in multiple systems, in the central nervous system, it appears as focal or multiple brain parenchymal damage[18, 19]. When affect large vessels, BD mainly act as cerebral venous sinus thrombosis[20]. Artery involvement is rare compared with venous involvement, manifesting as arterial stenosis and/or aneurysm formation which often leads to intracranial and/or subarachnoid hemorrhage or arterial infarction. [21-23].

Case Presentation

A 38-year-old man referred to our hospital due to a sudden numbness and weakness in his left extremities. Nervous system examination showed left hemiplegia, left limb stabbing algesia decreased and left cerebral lingual paralysis. Babinski sign positive on the left. Brain MRI showed focal ischemia in the right thalamus, and diffusion weighted imaging (DWI) showed high signal. Intracranial and cervical vascular imaging was normal (**Fig.1**). The patient was usually in good health and had no risk factors for cerebrovascular disease. Blood tests including C reaction protein (CRP), erythrocyte sedimentation rate （ESR）and immunogenic assays are normal. Based on the above findings, we first treated the patient with anti-cerebral infarction. The patient's symptoms improved and discharged from hospital.

Two months later, the patient developed dizziness, fatigue in both lower limbs, difficulty to walk and pain in both knees and left shoulder joints. The physical examination revealed the old and new rashes alternated on face, back and behind the ears (**Fig.2**), also scars at the intravenous site (**Fig.3**). The left limb was slightly hemiplegia, and stabbing algesia decreased. High-resolution MRI of brain suggested there were slightly thickened walls of the terminal portion of the left internal carotid artery, V4 segment of bilateral vertebral artery, P2 segment of the right posterior cerebral artery (**Fig.4**), the terminal portion of M1 segment of the right middle cerebral artery, M2 and M3 segments of bilateral middler cerebral artery, A2 segment of bilateral anterior cerebral artery. The enhancement scanning showed markedly enhanced signal, a double-track-like change, and a narrowed vascular lumen, suggested multiple intracranial arteritis. Hip MRI showed a long and flaky T1 weighted and T2 high fat-suppression signal on the lateral of left femoral head which suggested degenerative changes. The patient underwent genetic testing for hereditary cerebrovascular disease, (detected by Golden Field Medical, Inc., using analysis of missense mutations and alternative splicing. This lab has got the accreditation of College of American Pathologists.), and the result didn't show pathogenic variation. IL-8 252pg/ml (normal value:＜62pg/ml). The patient supplimented another medical history: repeated but mild oral ulcers and back rash over the years and probably also had genital ulcers. According to the diagnostic criteria, this case was diagnosed as BD. We then recommended the patient to do a pathological biopsy of the skin lesion, and the result

showed small vasculitis (**Fig.5**). We gave him colchicine and the rashes were relieved. We treated the patient with mycophenolate mofetil dispersible tablets (Seccopin), hydroxychloroquine tablets (Flush) and colchicine tablets. Within half a year, the patient's skin rash gradually alleviated, and the symptoms of oral ulcer and nervous system damage did not recur.

Discussion And Conclusions

This patient was initially diagnosed as acute cerebral infarction, and even the second admission was still manifested as cerebrovascular disease, but no obvious cause was found after routine examination for cerebrovascular disease. We considered the neurological damage was caused by the infarction of the deep small branches of the middle cerebral artery. Then the high resolution MRI of brain showed intima thickening on the intracranial and cervical arteries which suggested arteritis.

Cerebral infarction and vasculitis are uncommon symptoms in the course of BD, only two cases have been reported so far[15, 24]. In one case, neurological deficits were considered to be infarction in the deep perforating branch of middle cerebral artery, but it was not found in brain imaging. The other case was an autopsy study, it showed clearly that the infarction area was consistent with the occlusion regions resulting from arteritis of the middle cerebral artery branches[25]. Vascular involvement is a fatal complication to BD patients, so early diagnosis is very important.

A positive reaction to intravenous acupuncture was found at the early stage of our case while negative action to the skin pathery test. In the research of Hyun Kyu Chang et al, the responses of Pathergy test among 64 BD patients indicated that the skin Pathergy test has a certain specificity in BD diagnosis, but the sensitivity was not high. While intravenous Pathergy test seemed to be superior to the skin Pathergy test on both specificity and sensitivity. This article also stated that positive Pathergy test reactions usually occur during active periods of BD[26]. This hypothesis is consistent with the characteristic of our case.

Immune factors play a major role in the pathogenesis of BD, but ESR and CRP cannot be used as a criterion for active stage of the disease[27]. IL-8 acts as a neutrophil activationg factor in BD, attracts and activates leukocytes, then actives the immune system and alters endothelial cells. Many studies have reported that IL-8 level in plasma is elevated in BD patients[28]. Selda Pelin Kartal Durmazlar *et al*. found that IL-8 is positively correlated with the activity of BD, and also has a high correlation with the BD activity index and numbers of active symptoms[29]. There are still many other studies showed there is no significant relationship between IL-8 level and vascular involvement, while to this patient, he had frequent recurrence of rash and repeated central nervous system symptoms, and patient’s blood tests only showed the IL-8 level was increased, up to 4 times higher than normal. Therefore, we consider that IL-8 is associated with vascular involvement and can be a suggestion for activity of BD, also might be used as an indicator of BD for nervous system involvement. Then we repeatedly asked about the medical history, he reminded there were repeated rashes and oral ulcers after puberty, but these symptoms didn’t affect daily life. There was also an indeterminate history of genital ulcers, but he couldn’t remember the details

and the ulcers healed itself. For this patient, there was no risk factors for cerebrovascular disease in the past, and also no abnormalities in the genes and causes for stroke in the young. Fortunately, after excluding the above conditions and got the result that there was extensive cerebral artery intimal thickening from high-resolution MRI, we summarized the characteristics of patients, such as oral ulcers (2 points), skin lesions (1 point), neurological symptoms (1 point), central nervous system lesions (1 point), vascular symptoms (1 point) and Pathergy test (1 point), total score of 7 points, in line with the ICBD. So we can clearly diagnose this case as BD with cerebral arterial infarction caused by cerebral arteritis as early symptoms. In addition, we found plasma IL-8 level was significantly elevated at the early stage of this case, while ESR, CPR and other indicators have no obvious abnormalities.

Abbreviations

IL-8: Interleukin-8 NBD: Neuro-Behcet's disease

BD: Behcet's disease MRI: magnetic resonance imaging

MMF: Mycophenolate mofetil IL-1: Interleukin-1

TNF-α: tumor necrosis factor α DWI: diffusion weighted imaging

CRP: C reaction protein ESR: erythrocyte sedimentation rate

ISG: International Study Group ICBD: International criteria for Behcet's disease

Declarations

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Availability of data and materials

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Authors' contributions

HY, MMZ, and YS made substantial contributions to conception and design; HY, NS and SSL made substantial contributions to acquisition of data; HY, MMZ, YS and JH made substantial contributions to analysis and interpretation of data; HY, JH and JYT have been involved in drafting the manuscript or revising it critically for important intellectual content; All authors given final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for

appropriate portions of the content; All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

This study was approved by the institutional review board and ethics committee of Shandong Provincial Qianfoshan Hospital.

Consent for publication

Written informed consent was obtained from the patient for publication of this report and the figures.

Competing interests

The authors declare that they have no competing interests.

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References

1. Yazici H. Behcet's syndrome: an update. Current rheumatology reports. 2003;5 3:195-9.
2. Kural-Seyahi E, Fresko I, Seyahi N, Ozyazgan Y, Mat C, Hamuryudan V, et al. The long-term mortality and morbidity of Behcet syndrome: a 2-decade outcome survey of 387 patients followed at a dedicated center. Medicine (Baltimore). 2003;82 1:60-76.
3. Tsuruta D, Dainichi T, Hamada T, Ishii N, Hashimoto T. Molecular diagnosis of autoimmune blistering diseases. Methods in molecular biology (Clifton, NJ). 2013;961:17-32; doi: 10.1007/978-1-62703-227-8_2.
4. Direskeneli H. Behcet's disease: infectious aetiology, new autoantigens, and HLA-B51. Annals of the rheumatic diseases. 2001;60 11:996-1002.
5. Davatchi F, Shahram F, Chams-Davatchi C, Shams H, Nadji A, Akhlaghi M, et al. Behcet's disease: from East to West. Clinical rheumatology. 2010;29 8:823-33; doi: 10.1007/s10067-010-1430-6.
6. Cakir N, Dervis E, Benian O, Pamuk ON, Sonmezates N, Rahimoglu R, et al. Prevalence of Behcet's disease in rural western Turkey: a preliminary report. Clinical and experimental rheumatology. 2004;22(4 Suppl 34):S53-5.
7. Azizlerli G, Kose AA, Sarica R, Gul A, Tutkun IT, Kulac M, et al. Prevalence of Behcet's disease in Istanbul, Turkey. International journal of dermatology. 2003;42 10:803-6.

8. 10th APLAR Congress of Rheumatology. Journal of clinical rheumatology : practical reports on rheumatic & musculoskeletal diseases. 2002;8(4):216.
9. Papoutsis NG, Abdel-Naser MB, Altenburg A, Orawa H, Kotter I, Krause L, et al. Prevalence of Adamantiades-Behcet's disease in Germany and the municipality of Berlin: results of a nationwide survey. Clinical and experimental rheumatology. 2006;24(5 Suppl 42):S125.
10. Mohammad A, Mandl T, Sturfelt G, Segelmark M. Incidence, prevalence and clinical characteristics of Behcet's disease in southern Sweden. Rheumatology (Oxford, England). 2013;52 2:304-10; doi: 10.1093/rheumatology/kes249.
11. Criteria for diagnosis of Behcet's disease. International Study Group for Behcet's Disease. Lancet (London, England). 1990;335(8697):1078-80.
12. The International Criteria for Behcet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. Journal of the European Academy of Dermatology and Venereology : JEADV. 2014;28 3:338-47; doi: 10.1111/jdv.12107.
13. Knapp P. Die Technik der Staroperation. Schweizerische medizinische Wochenschrift. 1948;78(2):38.
14. Serdaroglu P. Behcet's disease and the nervous system. Journal of neurology. 1998;245 4:197-205.
15. Akman-Demir G, Serdaroglu P, Tasci B. Clinical patterns of neurological involvement in Behcet's disease: evaluation of 200 patients. The Neuro-Behcet Study Group. Brain : a journal of neurology. 1999;122 (Pt 11):2171-82.
16. Siva A, Kantarci OH, Saip S, Altintas A, Hamuryudan V, Islak C, et al. Behcet's disease: diagnostic and prognostic aspects of neurological involvement. Journal of neurology. 2001;248 2:95-103.
17. Kidd D, Steuer A, Denman AM, Rudge P. Neurological complications in Behcet's syndrome. Brain : a journal of neurology. 1999;122 (Pt 11):2183-94.
18. Reynolds N. Vasculitis in Behcet's syndrome: evidence-based review. Current opinion in rheumatology. 2008;20 3:347-52; doi: 10.1097/BOR.0b013e3282ff0d51.
19. Mendes D, Correia M, Barbedo M, Vaio T, Mota M, Goncalves O, et al. Behcet's disease-a contemporary review. Journal of autoimmunity. 2009;32 3-4:178-88; doi: 10.1016/j.jaut.2009.02.011.
20. Siva A, Saip S. The spectrum of nervous system involvement in Behcet's syndrome and its differential diagnosis. Journal of neurology. 2009;256 4:513-29; doi: 10.1007/s00415-009-0145-6.
21. Hamza M. Large artery involvement in Behcet's disease. The Journal of rheumatology. 1987;14(3):554-9.
22. Zelenski JD, Capraro JA, Holden D, Calabrese LH. Central nervous system vasculitis in Behcet's syndrome: angiographic improvement after therapy with cytotoxic agents. Arthritis and rheumatism. 1989;32 2:217-20.
23. Pannone A, Lucchetti G, Stazi G, Corvi F, Ferguson TL, Massucci M, et al. Internal carotid artery dissection in a patient with Behcet's syndrome. Annals of vascular surgery. 1998;12 5:463-7; doi: 10.1007/s100169900185.

24. Krespi Y, Akman-Demir G, Poyraz M, Tugcu B, Coban O, Tuncay R, et al. Cerebral vasculitis and ischaemic stroke in Behcet's disease: report of one case and review of the literature. European journal of neurology. 2001;8 6:719-22.
25. Nishimura M, Satoh K, Suga M, Oda M. Cerebral angio- and neuro-Behcet's syndrome: neuroradiological and pathological study of one case. Journal of the neurological sciences. 1991;106 1:19-24.
26. Chang HK, Cheon KS. The clinical significance of a pathergy reaction in patients with Behcet's disease. J Korean Med Sci. 2002;17 3:371-4; doi: 10.3346/jkms.2002.17.3.371.
27. Akkurt ZM, Bozkurt M, Ucmak D, Yuksel H, Ucak H, Sula B, et al. Serum Cytokine Levels in Behcet's Disease. Journal of clinical laboratory analysis. 2015;29 4:317-20; doi: 10.1002/jcla.21772.
28. Alpsoy E, Kodelja V, Goerdt S, Orfanos CE, Zouboulis Ch C. Serum of patients with Behcet's disease induces classical (pro-inflammatory) activation of human macrophages in vitro. Dermatology (Basel, Switzerland). 2003;206 3:225-32; doi: 10.1159/000068888.
29. Durmazlar SP, Ulkar GB, Eskioglu F, Tatlican S, Mert A, Akgul A. Significance of serum interleukin-8 levels in patients with Behcet's disease: high levels may indicate vascular involvement. International journal of dermatology. 2009;48 3:259-64; doi: 10.1111/j.1365-4632.2009.03905.x.

Figures

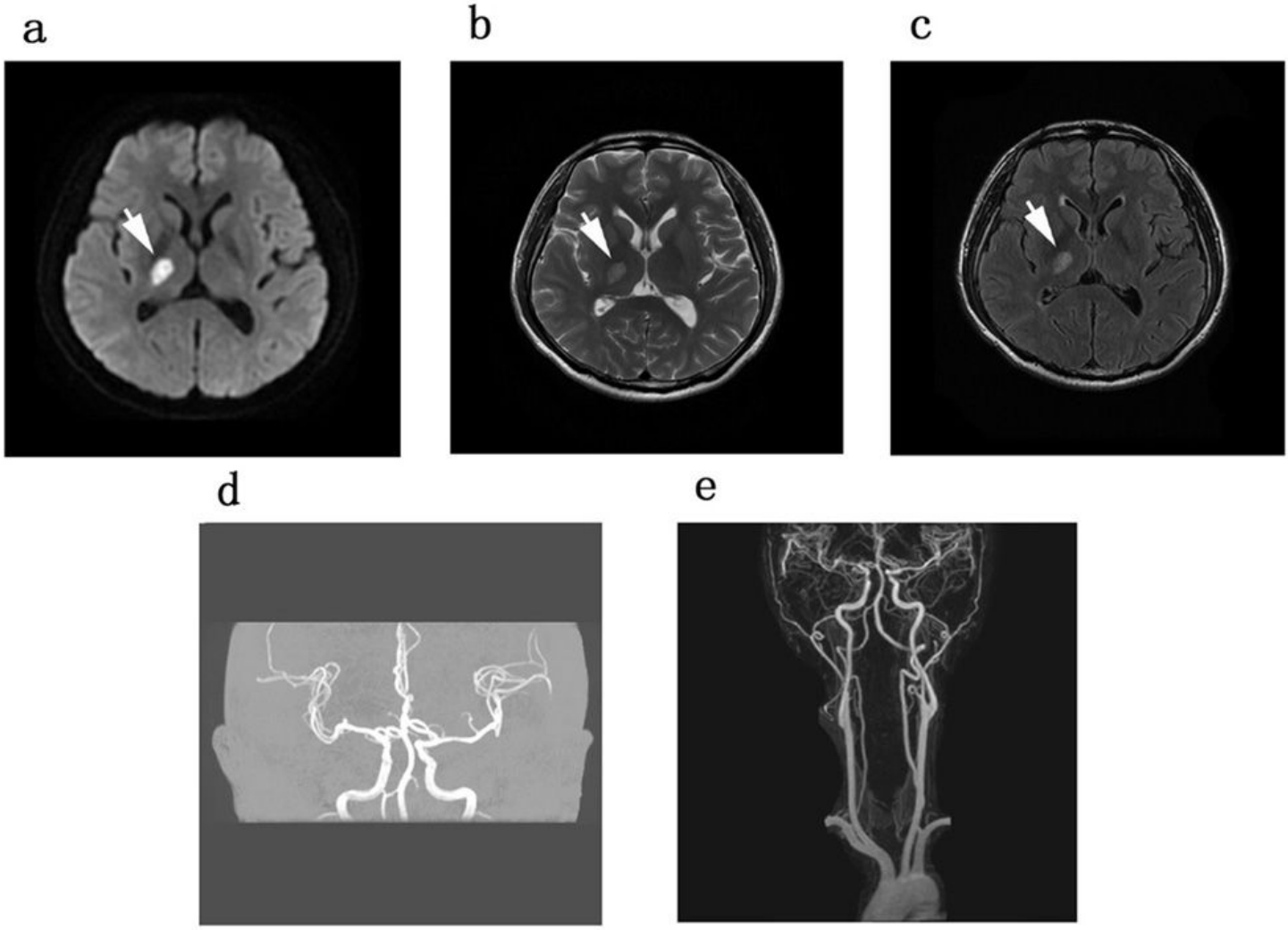

Figure 1

Brain magnetic resonance imaging (MRI). a.b.c. Diffusion weighted imaging (DWI) and T2 fluid-attenuated inversion recovery (FLAIR) imaging showed high signal, while long signal in T1 weighted imaging and T2 weighted imaging of the right thalamus. d.e. Magnetic resonance angiography of cerebral and carotid arteries was normal.

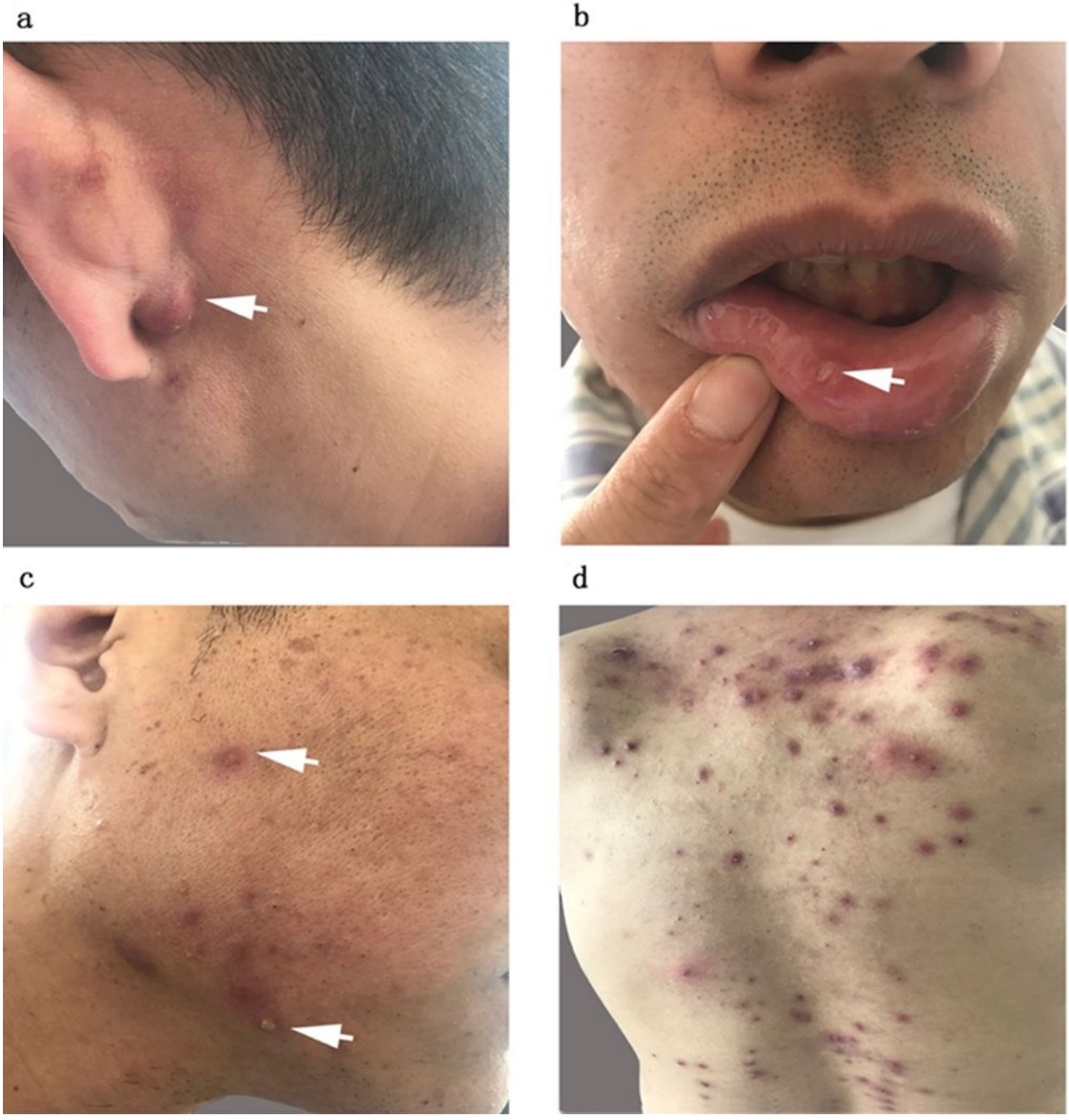

Figure 2

The old and new rashes alternated on face, back and behind the ears.

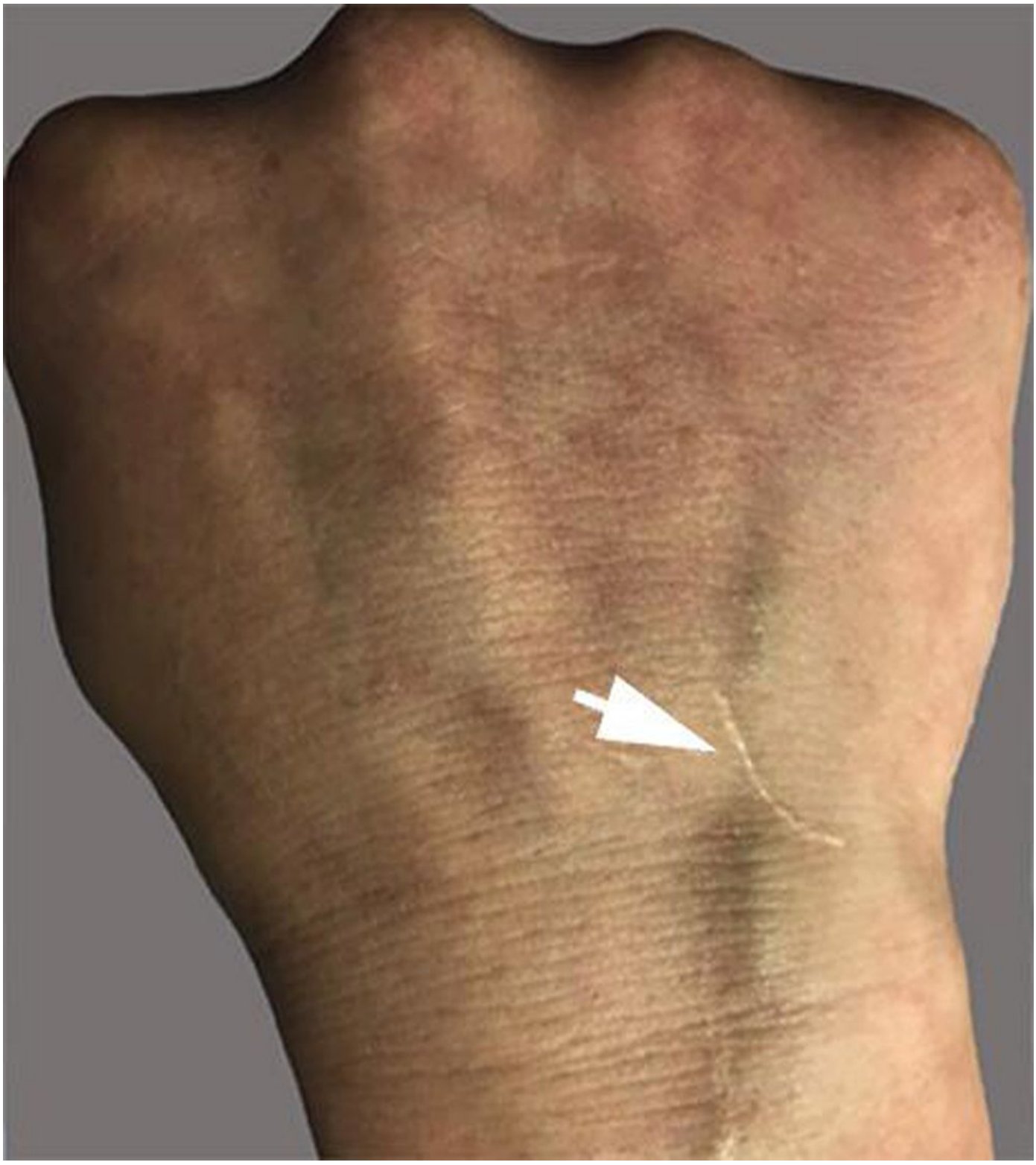

Figure 3

Scars at the intravenous site.

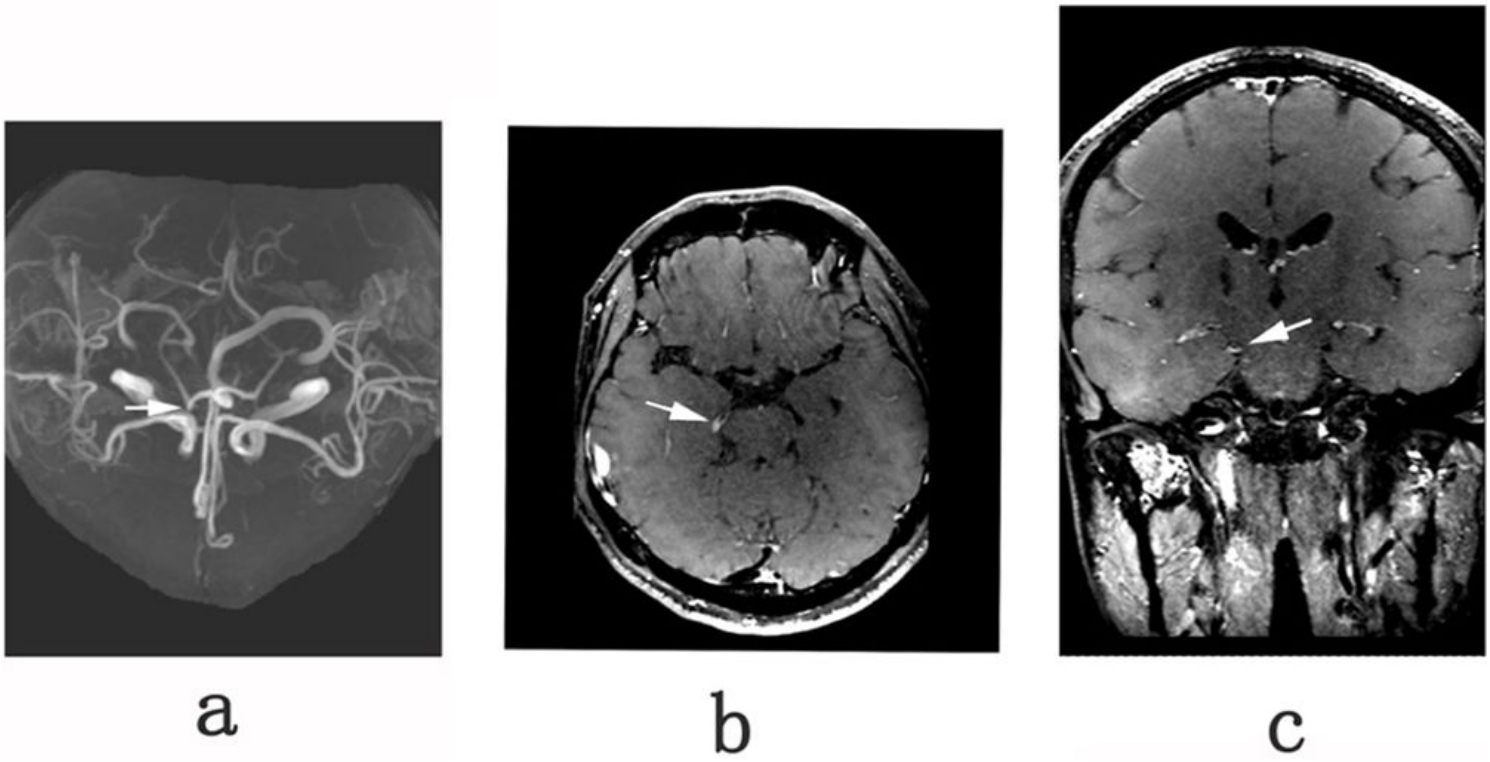

Figure 4

High-resolution MRI of brain showed the slightly thickened walls of the terminal portion of the right posterior cerebral artery.

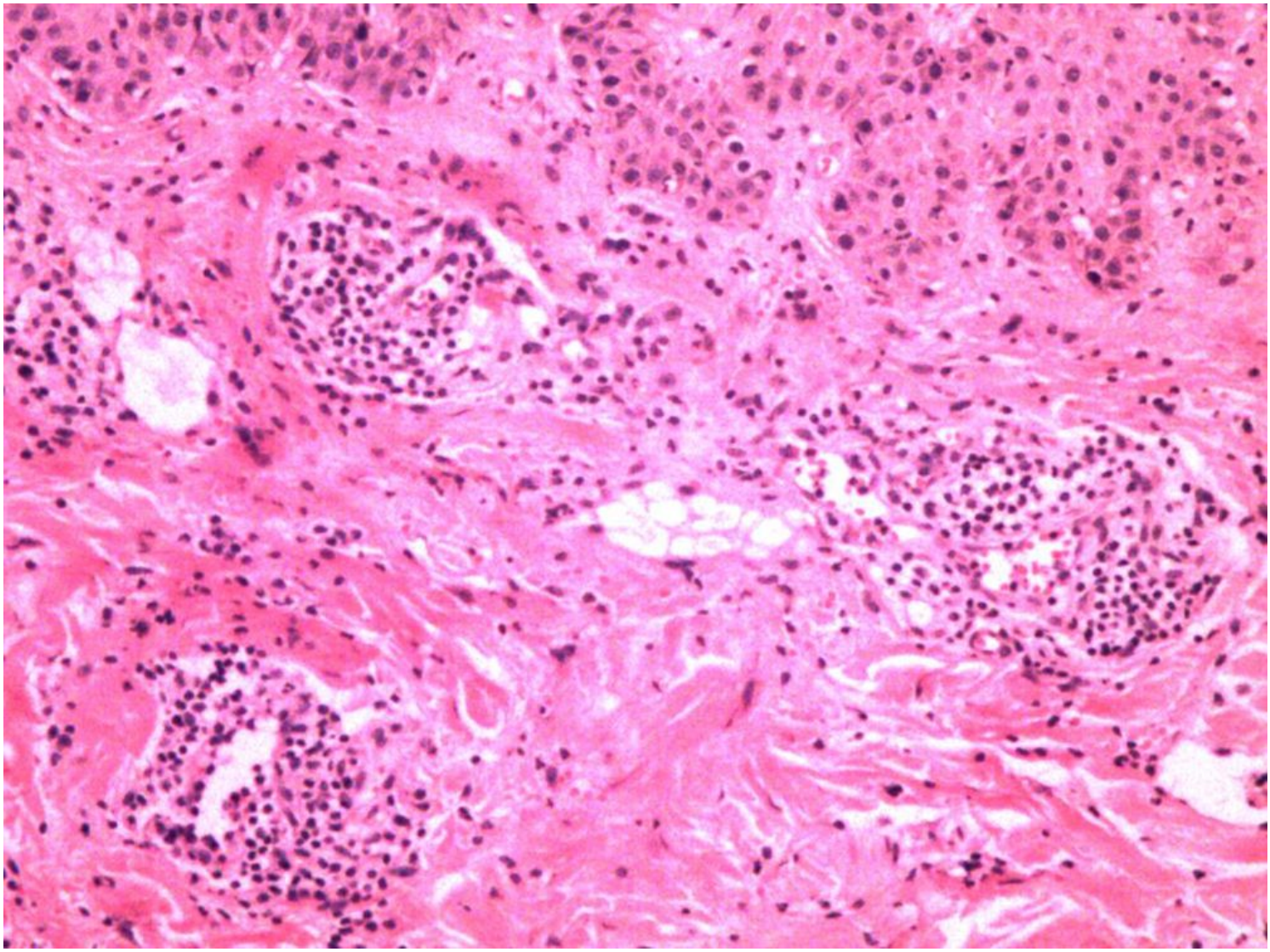

Figure 5

Pathological biopsy of the skin lesion showed small vasculitis.

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