Heliyon 10 (2024) e32173

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Case report

Indolent CD8-positive T-LPD of the peripheral nervous system in a 19-year-old man

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ARTICLE INFO

Keywords:
CD8
T-cell lymphoproliferative disorder
Neurolymphomatosis
Chronic inflammatory demyelinating polyneuropathy
Peripheral neuropathy

ABSTRACT

A 19-year-old man presented with recurrent intermittent fever, progressive limbs weakness, numbness, and atrophy for 5 years. Biopsy of the sural nerve, spleen, lymph nodes, bone marrow and labial gland revealed that monomorphic small lymphoid cells infiltrated diffusely and that there was severe loss of large myelinated nerve fibers. Immunohistochemically, these cells were mainly CD8-positive T cells and were positive for CD3 and CD57. This patient was diagnosed as indolent CD8-positive T lymphoproliferative disorder (indolent CD8-positive T-LPD), emphasizing the need for a broad differential diagnosis under these conditions, and nerve biopsy should be performed.

1. Introduction

Lymphoproliferative disorders (LPDs) are several conditions in which lymphocytes are produced in excessive quantities. They typically occur in people who have a compromised immune system. They are sometimes equated with "immunoproliferative disorders" [1]. According to the 5th edition of the World Health Organization Classification of Hematolymphoid Tumors (WHO-HAEM5), there are three types of tumor-like lesions with T-cell predominance: indolent T-lymphoblastic proliferation (ITLP), Kikuchi-Fujimoto disease (KFD) and autoimmune lymphoproliferative syndrome (ALPS) [2].

We report a patient who presented with chronic inflammatory demyelinating polyneuropathy (CIDP)-like neuropathy. Based on thorough clinical and pathological features, a diagnosis of CD8-positive indolent T-cell lymphoproliferative disorder (indolent CD8-positive T-LPD) of multiple organs was made.

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https://doi.org/10.1016/j.heliyon.2024.e32173
Received 14 February 2024; Received in revised form 28 May 2024; Accepted 29 May 2024
Available online 29 May 2024

2. Case presentation

A 19-year-old man presented with recurrent intermittent fever, progressive limb muscle weakness, numbness, and atrophy for the past 5 years. Initially, he developed clumsiness in the lower limbs, causing difficulty with running and jumping. Then, his muscle weakness worsened, and slowly progressed to the distal upper limbs. Atrophy was noted in the lower limbs and bilateral hands. In addition, he presented with abnormal sensation in four distal limbs. Splenomegaly and bilateral cataracts (cataracts treated surgically) were noted during this period. He reached his early milestones in motor and intelligence development at an appropriate age. Two years before admission, the patient reported blurry vision, as well as edema of the face and lips (Fig. 1A).

His elder brother had a normal developmental milestone and no history of immunodeficiency-related diseases before the age of 7. However, he had intermittent fever for 2 years and died at the age of 7 without a definitive diagnosis.

His vital signs were normal except for a low-grade fever of 38 °C upon admission. Ophthalmological examination revealed bilateral eyelid edema, ptosis, symmetrical eyelid closure weakness, a pupil diameter of 5 mm on the left side and 6 mm on the right side, and loss of the light reflex. Physical examination revealed facial edema and facial nerve paralysis. Neurological examination revealed that global cognitive function was normal. He had weakness in the distal four limbs: muscle strength of 0/5 in wrist flexor and extensor muscles, 0/5 in two-handed grip, and 0/5 in dorsiflexion and plantar flexor muscles. The proximal muscle strength was normal (5/5 on a medical research council scale graded 0–5). Muscle tone in the four limbs was reduced (0/4 on the modified Ashworth scale graded 0–4). Deep tendon reflexes were globally absent. Wrist drop, foot drop, and muscle atrophy were noted (Fig. 1B). Pathologic reflexes were negative on both sides. There was a presence of hypesthesia in a stocking-glove pattern with no sensory level.

An initial blood test revealed a high lymphocyte count (10.60×10^9/L, 51.71 %), whereas the leukocyte count (2.94×10^9/L) and platelet count (88×10^9/L) decreased. Epstein–Barr virus (EBV)-VCA IgG (>750.00 U/mL) was positive. Tests for EBV-VCA IgM, EBNA-IgG and EBV-DNA were negative. Cerebral spinal fluid (CSF) analysis and concomitant flow cytometry were normal. Other tests, including HIV, T-Spot, EBV-DNA, G-test and ANA\ENA\ANCA\APL, were negative. Whole exome sequencing (WES) was performed using DNA from the patient's blood and his family members' blood. However, no significant variants were detected. Abdominal ultrasonography revealed splenomegaly. Contrast-enhanced CT of the chest, abdomen, and pelvis revealed small nodules in the upper lobes of both lungs and multiple lymph nodes in the axillary, mesenteric, retroperitoneal, and inguinal areas. There was no significant abnormality on brain MRI. Thigh MRI showed revealed bilateral enlargement of the sciatic nerve and muscle atrophy (Fig. 1C). Electromyography in 2015 revealed slowed motor nerve conduction velocities in four limbs (MCV: 17.4–31.5 m/s), distal motor latency delay, decreased compound motor action potential (CMAP) amplitude, and widened motor unit potential (MUP) upon light contraction without fibrillation or positive sharp waves. EMG in 2018 revealed marked deterioration with loss of motor and sensory amplitudes, conduction block and slow conduction velocities in severely weak distal muscles.

We reviewed the pathology reports from all previous biopsy specimens performed since 2014, including the spleen, sural nerve, lymph nodes, bone marrow and labial gland. The origin of these impaired cells was confirmed by cellular morphology, immunostaining, and genetic analysis. The biopsy results are shown in Fig. 2 and Table 1.

Sural nerve biopsy showed a large amount of lymphocytic infiltration in the nerve bundles (Fig. 2A–C), which infiltrated and destroyed the nerve fiber bundles and small blood vessel walls. Electron microscopy (EM) revealed that the density of myelinated and unmyelinated fibers decreased tremendously without regeneration. Immunohistochemical staining revealed that the infiltrating lymphocytes were positive for CD2, CD3, CD4 (slightly), CD5, CD7, CD8 (dominantly), CD20 (partially), CD57, Bcl-2, Bcl-6 (partially), TIA-1, Granzyme B (fewly) and S100 and negative for MPO, CD117, CD 1α, TdT, CD79α, PAX-5, CD10, CD56, Cyclin D1, PMG-1, CD23 and EBER. A low proliferation index was detected for Ki-67 (20 %) (Fig. 2D–F).

The patient underwent splenectomy in the first two years. Pathology results of resected spleen specimens revealed lymphocytic infiltration, predominantly the T phenotype and has no structural abnormality. The cells were positive for CD3, CD4, CD5, CD8, CD20, CD38 and TIA-1 and negative for CD56, GB, mum 1, IgG4 and EBER1/2-ISH.

Multiple bone marrow biopsies revealed hypoplasia of hematopoietic cell granules, erythroid and myeloid hyperplasia, accompanied by lymphocyte proliferation (Fig. 2G). Infiltrating cells were positive for CD20, CD235a, CD3, CD5, and PAX-5.

Pathology of the inguinal lymph nodes revealed that cortical lymphatic follicles disappeared and that there was monomorphic

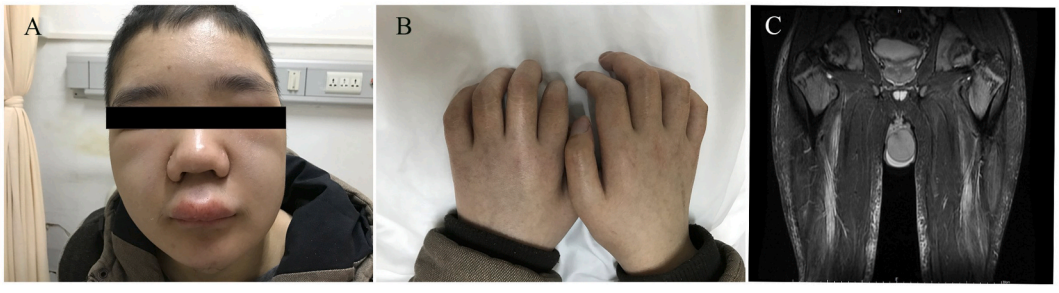

Fig. 1. Clinical characteristics and images
(A–B) Face (A) and hands (B) of the patient. (C) Thigh MRI on coronal STIR showed enlargement of the bilateral sciatic nerve. MRI, magnetic resonance imaging; STIR, short-tau inversion recovery.

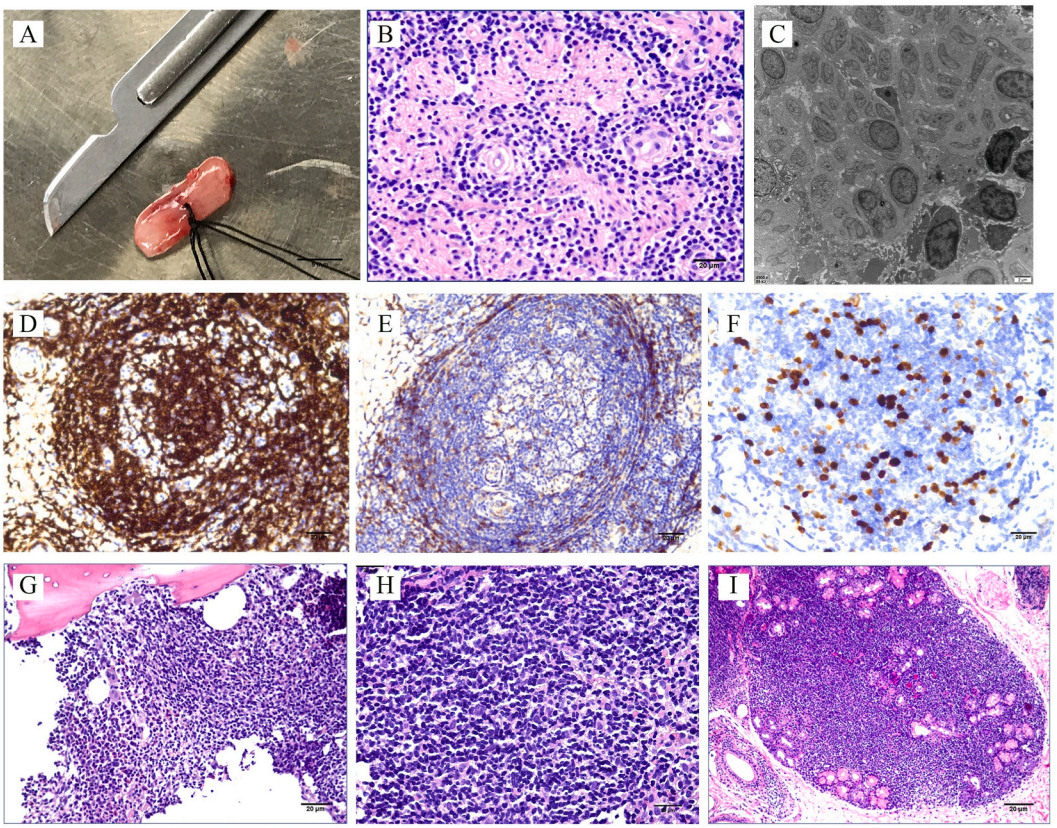

Fig. 2. Biopsy results
(A-E) Peripheral nerve pathology of the patient showed swelling, approximately 5 mm in diameter (A), lymphocytic infiltration and decreased density of unmyelinated fibers by H&E staining (B) and electron microscopy (C). The lymphocytic cells were mainly CD8-positive (D) and were accompanied by small amounts of CD4 (E). The proliferation fraction, as determined by Ki-67 staining, was low (F). (G) Biopsy results of the bone marrow revealed the presence of active myelodysplasia and lymphocyte proliferation. (H) Pathological assessment of the lymph nodes demonstrated monomorphic small-sized T lymphoproliferative infiltration. (I) Biopsy of the labra gland revealed lymphocytic infiltration predominantly distributed around the small vessels, and the amount of filter foam was significantly reduced. Scale bars: A: 5 mm; B: 20 μm; C: 2 μm, D–H: 20 μm.

small-sized monotonous T lymphoproliferative infiltration (Fig. 2H). Immunohistochemical staining revealed that lymphatic cells were positive for CD3, CD5, CD2, CD7, CD8, CD4 (partially), Bcl-2, TIA-1, Granzyme B (fewly), CD20 (weakly), Bcl-6 (weakly), C-myc (<5 %), and Ki67 (8 %).

The biopsy results of the swollen upper lip (labra gland) showed lymphocytic infiltration predominantly distributed around the small vessels, and the amount of filter foam was significantly reduced (Fig. 2I). The lymphoid cells were positive for CD3, CD5, CD43, CD8, CD4 (fewly), CD20 (weakly), and Bcl-2 and negative for AE1/AE3, CD10, CD21, CD23, Kappa, Lambda, Bcl-6, IgG4, CD138, CD35, Cyclin D1, and CD79α.

In addition, T-cell receptor (TCR) gene rearrangement was detected in the bone marrow, spleen, sural nerve, lymph nodes and labial gland. EBER was negative in all biopsy areas except for the labial gland.

Symmetric sensory disturbance in the distal limbs (stocking-glove hypesthesia) and lower motor neuron paralysis (flaccid quadriparesis, ophthalmoplegia and facial palsy) are manifestations of polyneuropathy. Multiple systems, including the spleen, bone marrow, skin and cornea, were involved. For patients with a chronic course of these symptoms, differential diagnoses included autoimmune-mediated inflammatory diseases, infectious diseases, metabolic disturbances, and neoplastic or paraneoplastic syndromes, such as chronic inflammatory demyelinating polyneuropathy (CIDP), HIV or EBV, lymphoma, paraneoplastic autoimmune multiorgan syndrome (PAMS) [2].

Given the evidence of clinical, morphological, immunophenotypic and cytogenetic characteristics, the above diagnoses were ruled out, and indolent CD8-positive T-LPD of multiple organs was diagnosed [3,4]. The patient was treated intermittently with steroids for 5 years after the first bone marrow biopsy suggested LPDs. In the interim, his symptoms were partially relieved, and he relapsed and progressively deteriorated. After the diagnosis, he was treated with cyclosporine A for 4 months. Considering the poor prognosis due to extensive infiltration of peripheral and cranial nerves, cyclophosphamide and methotrexate were also given. Three years later, the patient died from the exacerbation of multisystem lesions or transformation into neurolymphomatosis. The case report timeline is presented in Fig. 3.

Table 1
Pathology reports of all previous biopsy specimens.

biopsy site	Time	Histology	Immunohistochemical and molecular findings
Sural nerve	2018–12	A large amount of lymphocytic infiltration in the nerve bundles	CD2 (+), CD3 (+), CD4 (slightly +), CD5 (+), CD7 (+), CD8 (+), CD20 (partially +), Bcl-2 (+), Bcl-6 (partially +), CD57 (+), TIA-1 (+), Granzyme B (fewly +), S100 (+). Ki67 (20 %). MPO (−), CD117 (−), CD 1α(−), TdT (−), CD79α(−), PAX-5 (−), CD10 (−), CD56 (−), Cyclin D1 (−), PMG-1 (−), CD23 (−), EBER (−). TCR (+).
spleen	2016–7	T lymphocytic infiltration	CD3 (+), CD5 (partially +), CD4 (partially +), CD8 (partially +), CD38 (+), TIA-1 (partially+). CD56 (−), Granzyme B (−), mum 1 (−), IgG4 (−), EBER (−). TCR γ (+).
bone marrow	2016–2	The proportion of granulocyte and erythrocyte was generally normal, scattered lymphocytes were found in hematopoietic tissue	CD3 (partially +), CD5 (partially +), CD20 (individually +), CD235a (partially +), PAX-5 (individually +), TCRδ (+).
	2016–7	The proliferation of hematopoietic granulocytes and megakaryocytes was active with a small number of lymphoid cells.	CD4 (partially +), CD8 (partially +), CD3 (+), CD5 (partially +), CD38 (+), TIA-1(partially +). CD56 (−), Granzyme B (−), mum 1 (−), IgG4 (−), EBER (−). TCRγ (+).
	2019–4	Hypoplasia of hematopoietic cell granules, erythroid and myeloid hyperplasia, accompanied by lymphocyte proliferation	CD3 (+), CD5 (+), CD2 (+), CD7 (+), CD8 (+), CD4 (partially +), Bcl-2 (+), TIA-1 (+), Granzyme B (fewly +), CD20 (slightly +), Bcl-6 (slightly +). C-myc (<5 %), Ki67 (8 %). CD10 (−), CD21 (−), CD35 (−), CD79α (−), CD30 (−), CD34 (−), CD117 (−), TDT (−), CD56 (−), MUM-1 (−), PGM-1 (−), HHV8 (−), EBER (−). TCRαβ (−), TCRγδ (−).
	2019–11	Hematopoietic cell proliferation was basically normal range	NA
labra gland	2019–4	Lymphocytic infiltration predominantly distributed around the small vessels, and filter foam was significantly reduced	CD3 (+), CD5 (+), CD43 (+), CD8 (+), CD4 (partially +), CD20 (weakly +), Bcl-2 (+), IgG (weakly +), EBER (individually +). Ki67 (8 %). AE1/AE3 (−), CD10 (−), CD21 (−), CD23 (−), Kappa (−), Lambda (−), Bcl-6 (−), IgG4 (−), CD138 (−), CD35 (−), Cyclin D1 (−), CD79α (−). TCR (+).
inguinal lymph nodes	2019–4	Cortical lymphatic follicles disappeared and monomorphic small-sized monotonous T lymphoproliferative infiltration	CD3 (+), CD5 (+), CD2 (+), CD7 (+), CD8 (+), CD4 (partially +), Bcl-2 (+), TIA-1 (+), Granzyme B (fewly +) CD20 (weakly +), Bcl-6 (weakly +). C-myc (<5 %), Ki67 (8 %). CD10 (−), CD21 (−), CD35 (−), CD79α (−), CD30 (−), CD34 (−), CD117 (−), TDT (−), MPO (−), CD235 (−), CD42b (−), CD56 (−), MUM-1 (−), PGM-1 (−), HHV8 (−), EBER (−). TCRαβ (−), TCRγδ (−).

TCR: T-cell receptor; EBER: Epstein-Barr virus-encoded RNA; TIA-1: T cell intracellular antigen 1; NA: not available. +: positive; -: negative.

3. Discussion

Indolent CD8-positive T-LPD is a rare type of low-grade clonal lymphoid proliferation. The disease mainly needs to be differentiated from neurolymphomatosis and other subsets of LPDs.

Neurolymphomatosis is a rare and generally devastating condition that can affect any part of the peripheral nervous system, leading to a wide range of presentations [5]. Necrosis, angiocentricity, angioinvasion and EBER positivity are characteristic features of this aggressive lymphoma [6]. In contrast to T lymphoblastic lymphoma/leukemia, indolent CD8-positive T-LPD has overt atypia or immunophenotypic abnormalities, monoclonality, and destructive/infiltrative patterns. In addition, contrary to the aggressive course

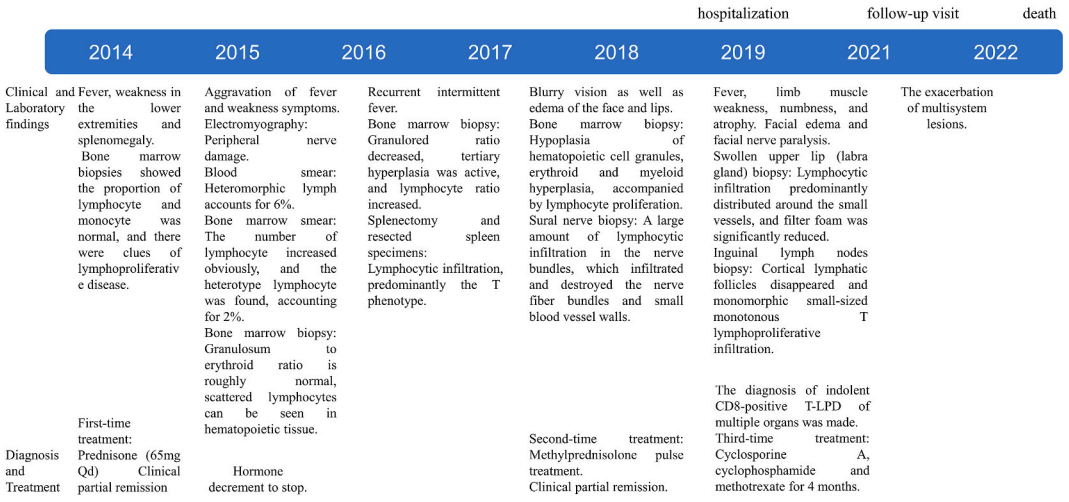

Fig. 3. Case report timeline.

of neurolymphomatosis, the indolent clinical course of T-LPD can also be retrospectively used to support the diagnosis.

LPDs occur at an increased rate in immunosuppressed patients and are often associated with EBV infection, which can induce many T/NK-cell LPDs [7]. In this case, the patient had some conditions, such as intermittent fever in her older brother for 2 years leading to death at age 7, and there could be an underlying inborn immune error. However, he had no history of immunosuppression before he began taking prednisone for treatment, and EBV-DNA was negative. There is not enough evidence to support a diagnosis of EBV-T/NK-LPDs and immunodeficiency-associated LPDs. In addition, his elder brother's medical history was mentioned in the family history, so inherited factors, such as ALPS, need to be considered. The two necessary conditions for the diagnosis of ALPS are a chronic disease course of more than 6 months and negative results for both CD4 and CD8 [8]. However, WES of our patient did not reveal the exact causative gene, and immunohistochemical staining revealed CD8 positivity.

Cases of indolent T-cell LPD of the gastrointestinal tract have been reported, and most of them had a CD8-positive immunophenotype [9–11]. Four patients had extra-gastrointestinal involvement, which involved the bone marrow, lymph nodes, and uterus [10, 12–15]. As described in our case, the lymphoid infiltrate observed in indolent CD8-positive T-LPD lesions is dense, nondestructive in architecture, and predominantly composed of small, immature lymphocytes and angioinvasive destruction without necrosis. Immunohistochemistry showed that the lymphocytes were derived from CD8-positive T cells. The Ki-67 proliferation index was very low (8 %). All these patients had a long follow-up with an indolent clinical course and protracted or relapsed disease without progression, as confirmed by repeated biopsies.

Proliferative disorders of CD8-positive T cells can result in diverse, benign or malignant clinical outcomes, necessitating the selection of an appropriate treatment modality. The most important characteristic of CD8-positive T-LPD is its indolence, as the most often recommended strategy is a careful "watch and wait" approach with no chemotherapy or radiation [16]. However, our young patients suffered from severe motor-sensory peripheral neuropathy. Therefore, immunosuppressive therapy was applied for treatment.

There are no characteristic manifestations of indolent CD8-positive T-LPD, and this disease is easily misdiagnosed as neurolymphomatosis or other subsets of LPDs, which poses great challenges for both clinicians and pathologists.

4. Conclusion

In summary, the patient initially presented with severe peripheral neuropathy, accompanied by the involvement of multiple systems, including the spleen, bone marrow, skin, and cornea. The pathology was dominated by CD8-positive T-cell infiltration. CD8-positive T-LPD may be present at more diverse sites than those described to date. This is the first case of CD8-positive T-LPD of the peripheral nervous system. Despite their rarity, understanding their existence is critical for preventing the misdiagnosis of neurolymphomatosis and avoiding unnecessary therapy.

Consent

Written informed consent was obtained from the individuals for the publication of any potentially identifiable images or data included in this article.

Sources of funding

This project is supported by the National Natural Science Foundation of China (No. 81870889 and 81571086), the Basic Research Project of Shanghai Sixth People's Hospital (ynms202209), the Shanghai Science and Technology Innovation Action Plan (23DZ2291500) and the Scientific Research Project Fund of Colleges and Universities in Anhui Province (2022AH050680).

Data availability statement

No data was used for the research described in the article.

Ethics statement

The ethics committee of Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine approved the study, with the approval number: 2021-219.

CRediT authorship contribution statement

Xiaowei Zhu: Writing – original draft, Data curation. **Benyan Zhang:** Writing – original draft, Data curation. **Xiaolong Jin:** Methodology, Investigation, Data curation. **Liche Zhou:** Data curation. **Li Cao:** Methodology, Funding acquisition, Data curation, Conceptualization. **Hui Yu:** Writing – review & editing, Supervision, Investigation. **Xinghua Luan:** Writing – review & editing, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to

influence the work reported in this paper.

Acknowledgements

The authors gratefully acknowledge the patient and his family for their collaboration, as well as Jie Yang from the Core Facility of Basic Medical Sciences, Shanghai Jiao Tong University School of Medicine for helping with electron microscope observation.

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