Heliyon 9 (2023) e22632

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Adult-onset Mendelian Susceptibility to Mycobacterial Diseases: A case report and systematic literature review

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ARTICLE INFO

Keywords:
Adult-onset
Inborn errors of immunity (IEIs)
Mendelian susceptibility to mycobacterial disease (MSMD)
Mycobacterium
Recombinant human interferon γ ((IFN-γ)

ABSTRACT

Objectives: To help in diagnosis and treatment of adult-onset Mendelian Susceptibility to Mycobacterial Disease (MSMD).
Methods: We reported a 27-year-old man who had disease onset at 18 years. Then we reviewed previous reports of adult-onset MSMD patients, and summarized their clinical characteristics.
Results: The case was diagnosed as MSMD with tyrosine kinase 2 (TYK2) mutation and had dramatic improvement after treatment. In addition to our presented case and through a review of the literature, 12 cases in total were included in our study. Average age of disease onset was 29.4 years. Medium delay of diagnosis was 2.5 years. Four were with IFN-γR1 deficiency, four with IL-12β1 deficiency, two with NEMO deficiency, one with TYK2 deficiency and one with STAT1 deficiency. Common symptoms were lymphadenopathy (6/12, 50.0 %), weight loss (6/12, 50.0 %), bone/joint pain (5/12, 41.7 %), fever (4/12, 33.3 %) and gastrointestinal symptoms (4/12, 33.3 %). Mycobacteria caused infections in lymph nodes (7/12, 58.3 %), bone/joint (5/12, 41.7 %) and skin (5/12, 41.7 %). After treatment, eight (66.7 %) got favorable prognosis, two (16.7 %) died and one (16.7 %) was unknown.
Conclusions: Adult-onset MSMD have complex clinical presentations and are difficult to recognize, which results in delayed diagnosis. However, once identified, antibiotics and IFN-γ might have good efficacy. Therefore, when encountering adult patients with recurrent and refractory mycobacterial infections, especially in lymph nodes, bone/joints, and skin, MSMD should be considered.

1. Introduction

Mendelian Susceptibility to Mycobacterial Disease (MSMD) is an inborn error of immunity (IEI) due to molecular defects in the interleukin 12 (IL-12)/interferon γ (IFN-γ) dependent signaling pathway. It is a rare disease with an incidence of about 2.0/per 100,000 [1]. Patients are highly susceptible to weakly virulent mycobacteria infections such as environmental mycobacteria. Also, they may be susceptible to more virulent pathogens such as *Salmonella*, *Mycobacterial tuberculosis*, and *Candida*, as well as endemic fungi (*Histoplasmosis, Coccidioides*). Nevertheless, infections caused by most other microbes generally do not occur [2–5]. MSMD occurs

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https://doi.org/10.1016/j.heliyon.2023.e22632
Received 30 April 2023; Received in revised form 15 November 2023; Accepted 15 November 2023
Available online 25 November 2023

mostly in children, but occasionally in adulthood (≥18 years). Since the first patient with confirmed gene mutation was reported in 1996 [6], about 600 patients in total were reported [1,7]. Among them, only 11 cases had disease onset during adulthood [8–15], accounting only about 0.2 %. Here we report an adult-onset MSMD patient and have performed a literature review, to raise physicians' awareness of this disorder in settings of adults.

2. Case presentation

A 27-year-old man complained of abdominal distension and weight loss for three months. He had a history of BCG vaccination at infant without adverse effects and was healthy before the age of 18 years. He had no siblings. His parents were healthy and are not consanguineous. At the age of 18 years (2011), he was clinically diagnosed with tuberculosis for cough, positive T-SPOT. TB and "nodular lesions with exudation in the posterior segment of the right upper lobe" on chest computerized tomography (CT) scan. He was cured after standard treatment, which was a combination of isoniazid, rifampicin, pyrazinamide and ethambutol (i.e., HRZE) for 2 months followed by isoniazid and rifampicin (i.e. HR) for 4 months, administered daily. At the age of 22 years (2015), he complained about persistent dry cough, and a chest CT scan revealed cavitary lesions in the posterior segment of the right upper lobe, the diagnosis of tuberculosis was made again and 2HRZE/4HR was prescribed. Though persistent dry cough was relieved after six months of medication, the original lung lesions got worse and new lesions appeared in the apical segments of the upper lungs as well as the dorsal segment of the right lower lung. Nevertheless, he refused further anti-tuberculosis treatment. At the same time, the patient developed erythema nodosum on the extremities and was diagnosed with cellulitis, which was later cured by antibiotics. Two months later, he developed arthralgia and was diagnosed with rheumatoid arthritis. Arthralgia was soon relieved with treatment. Another two months later, at the age of 23 years (2016), he got a persistent fever and cough. Positron emission tomography (PET)-CT demonstrated multiple active metabolic nodular mass shadows in bilateral lungs and multiple lymph nodes with enhanced metabolism. At that time, the high possibility of infection was considered, while lymphoma was not excluded. After empirical *anti*-mycobacteria and anti-fungal treatment, symptoms improved much. At age 25 (2018), the patient received episodes of antibiotics for recurrent fever. In October 2018, he developed pericarditis, hepatomegaly, splenomegaly, abdominal and pelvic effusion as well as hydronephrosis, and infection of non-tuberculous mycobacteria was considered. Then he took anti-non-tuberculous mycobacterial drugs for three months, without good efficacy. At age 26 (2019), a percutaneous lung biopsy was performed. There was chronic active inflammation, active alveolar epithelial hyperplasia, and regional epithelial non-typical adenomatous hyperplasia. In the previous years, many times of microbiologic tests including sputum smear and sputum cultures found no positive results. At age 27 (2020), a CT scan showed more and broader lesions appeared in his lungs. Percutaneous lung biopsy was performed again, along with next-generation sequencing (NGS), which demonstrated *Mycobacterium chelonae* and *Mycobacterium gordonae*, each had copy numbers >7000/mL. Regimen compromised with ethambutol, clarithromycin, linezolid, meropenem, and amikacin was prescribed. However, he could not tolerate the adverse effects and stopped taking the medication.

In July 2020, the patient was admitted to our hospital for abdominal distension and weight loss of 10 kg (kg). He was 173 cm (cm) tall and weighed 45 kg. A complete blood test showed a white blood cell count of 13.7×10^9/L (range: 3.5–9.5 $\times$ 10^9/L) and hemoglobin was 69 g/L (range: 90–130 g/L). The Biochemical profile displayed albumin of 29 g/L (range: 40–55 g/L). Other results were not remarkable. Both T-SPOT. TB and tuberculin skin test (TST) was positive. No significant results were found in routine immunological tests. An abdominal ultrasound scan confirmed massive ascites and hepatosplenomegaly. The CT scan showed scattered infection lesions in the bilateral lungs, mediastinal multiple enlarged lymph nodes, a small amount of pericardial effusion, and pleural effusion on the right side. We performed NGS in his peripheral blood as well as in his parents', which found he carried TYK2 mutations (G997A acquired from mother and C10T acquired from father). Therefore, he was diagnosed with MSMD (TYK2 mutation), non-tuberculous mycobacterial lung disease. He was administered with intravenous immune globulin (10 g, qd $\times$ 7 days) [16], dexamethasone (10 mg, qd $\times$ 5 days), IFN-γ (1 million U, biw), meropenem, compound sulfamethoxazole, and supportive treatment. Ten days later, the patient improved much and was discharged with the only prescription of IFN-γ (1 million U, biw). After two months of follow-up, his condition improved significantly. He was evaluated in January 2022 for the last time and was still receiving IFN-γ regularly, in good health.

3. Methods

1) Databases and Search Strategy

We conducted a systemic literature review of English and Chinese articles on MSMD patients with adulthood onset which published between 1981 and 2022. We searched English databases PubMed and Google Scholar using the keyword of "Mendelian Susceptibility to Mycobacterial Disease" or "MSMD". And searched Chinese databases (China National Knowledge Internet, Wanfang Data, and China Science and Technology Journal Database) using the following keywords (Chinese): "Mendelian Susceptibility to Mycobacterial Disease", "Mendelian Inheritance" and "Mycobacterial Disease". In addition, references were also reviewed for each article.

2) Selection Criteria (inclusion and exclusion criteria) and Data Extraction

Only case reports, case series and correspondence articles that reported individual-level data on the adult-onset MSMD patients were considered for the review. Studies were excluded if no original empirical data on the clinical manifestation of the condition was provided. The title, abstract, and full-text screening were completed in duplicate and independently by two reviewers (Yang and Xia).

Table 1
Reported cases with adult-onset MSMD.

Reference	Sex	Onsetage(yrs)	BCGvaccination	Diagnosisdelay(yrs)	Clinicalmanifestations	Infectedtissues	Pathogen	Defectedgenes(mutation)	Inheritance	Functionalimpairment	Treatment	Prognosis
Our case	M	18	Yes	9	cough, erythema nodosum, arthralgia, fever, abdominal distension, weight loss	lymph node, joint, skin, lung	*M. chelonae, M. gordonae*	TYK2 (G997A, C10T)	AR	C	antibiotics, IFN-γ, DXM, IVIG	good
Sakai [8]	M	39	N/A	1	lymphadenopathy	lymph node	*M. avium*	IL12RB1 (R213W)	AR	C	antibiotics, IFN-γ	N/A
Arend [9]	F	25	Yes	16	lymphadenopathy, arthralgia, myalgia, erythema nodosum, ostealgia, skin lesions (fistula, sinus)	lymph node, bone, joint, skin, tendon sheath, muscle	*M. avium, M. gordonae*	IFNGR1 (818del4)	AD	P	antibiotics	good
	F	29	N/A	1	lymphadenopathy, arthralgia, weight loss, fever, night sweat	lymph node, bone, joint, muscle	*M. avium*	IFNGR1 (818del4)	AD	P	antibiotics, IFN-γ	good
	F	24	Yes	34	lymphadenopathy, erythema nodosum	lymph node, skin	*M. asiaticum*	IFNGR1 (818del4)	AD	P	antibiotics	good
Remiszewski [10]	F	20	Yes	1	ostealgia, fever, fatigue, cough	bone, skin, lung, brain	*M. avium*	IFNGR1 (I87T)	AR	P	antibiotics, IFN-γ, DXM, spondylodesis	good
Tabarsi [11]	M	30	Yes	3	fever, hepatosplenomegaly, night sweat, lymphadenopathy, cough, weight loss, diarrhea	lymph node, gastrointestinal tract	*M. tuberculosis* (MDR-TB)	IL12RB1 (T355del)	AR	C	antibiotics, IFN-γ	death
Schejbel [12]	M	47	Yes	2	abdominal pain, diarrhea, weight loss	gastrointestinal tract	*M. branderi*	IL12RB1 (R283*X*)	AR	C	antibiotics, IFN-γ	good
Hsu [13]	M	34	N/A	N/A	skin lesions, weight loss, sigmoid obstruction	skin, gastrointestinal tract, mediastinum	*M. avium*	NEMO IKBKG (splicing mutation)	XR	P	antibiotics, IFN-γ, diverting colostomy	poor (has not cleared infection till publication)
	M	26	N/A	N/A	lymphadenopathy, weight loss	lymph node, lung, blood	*M. avium*	NEMO IKBKG (splicing mutation)	XR	P	antibiotics, IFN-γ	death
Taur [14]	F	25	Yes	N/A	N/A	N/A	*Salmonella*	IL12RB1 (K596E)	AR	C	antibiotics	good
Bhattad [15]	F	36	Yes	N/A	ostealgia	bone	*M. tuberculosis*	STAT1 (G250E)	AD	P	antibiotics	good

Dexamethasone: DXM.
IVIG: intravenous immune globulin.

The senior author (Lu) made the final decision if there was disagreements regarding the inclusion of studies for data extraction. Duplicate studies were removed. We collected data on gender, onset age, BCG vaccination, diagnostic delay, clinical manifestations, infected tissues, pathogen, defected genes, type of inheritance, functional impairment, treatment regimen, and prognosis.

3) Quality Assessment

The NIH Quality Assessment Tool [17] was used to assess the quality of included papers. Two reviewers independently conducted the assessment (Yang and Xia), and the senior author (Lu) made the final decision if there was disagreement. Finally, eight English articles and no Chinese articles were included in this study. (Table 1). This study was approved by the Ethics Committee of Shanghai Public Health Clinical Center, with ethics approval reference [2020-S150-01].

4. Results

Through the literature review, there were 283, over 500 and 21 manuscripts being retrieved from PubMed, Google Scholar, and the Chinese databases, respectively. We reviewed the most related 500 papers from the Google Scholar and all the other papers. Of the reviewed papers, eight studies were found eligible and considered for data extraction (Diagram 1). Four papers were case reports [8, 10–12], three were case serials [9,13,15] and one was original cohort study [14]. With the NIH Quality Assessment Tool, seven studies including our case were rated as fair and one was rated as good. The detailed results of the quality assessment are provided in Supplementary file S1. Eleven patients with adult-onset MSMD were described in previous publications. They are listed in Table 1 together with our case. In all the 12 cases, half were males. The average age of disease onset was 29.4 years (range: 18 to 47). The duration of the diagnosis delay was known in eight cases and the medium was 2.5 years, while the longest was 34 years. Eight patients were vaccinated with BCG in an infant. However, unlike MSMD children who are more prone to BCG disease [14,18], none of these BCG-vaccinated cases had developed BCG disease. Adult-onset MSMD patients have diverse clinical manifestations. Mainly were lymphadenopathy (6/12, 50.0 %), weight loss (6/12, 50.0 %), bone/joint pain (5/12, 41.7 %). Besides, fever (4/12, 33.3 %), gastrointestinal symptoms (4/12, 33.3 %), cough (3/12, 25.0 %), erythema nodosum (3/12, 25.0 %) were also observed, as well as other symptoms like night sweat, fatigue, myalgia, fistula, sinus, and hepatosplenomegaly. Nine got the environmental mycobacterial infection, two got *Mycobacteria tuberculosis* and one got *Salmonella*. Of those infected with environmental mycobacteria, six were infected with *Mycobacterium*

Table 2
Clinical Characteristics of the 12 adult-onset MSMD.

Chracteristics		number (%)
Clinical manifestations	lymphadenopathy	6 (50.0 %)
	weight loss	6 (50.0 %)
	bone/joint pain	5 (41.7 %)
	fever	4 (33.3 %)
	gastrointestinal symptoms	4 (33.3 %)
	cough	3 (25.0 %)
	erythema nodosum	3 (25.0 %)
	others	7 (58.3 %)
Pathogen	*Mycobacterium avium*	6 (50.0 %)
	Mycobacteria tuberculosis	2 (16.7 %)
	Mycobacterium gordonae	2 (16.7 %)
	Mycobacterium chelonae	1 (8.3 %)
	M. asiaticum	1 (8.3 %)
	Mycobacterium branderi	1 (8.3 %)
	Salmonell	1 (8.3 %)
Infected Tissues	lymph nodes	7 (58.3 %)
	bone/joint	5 (41.7 %)
	skin	5 (41.7 %)
	lungs	3 (25.0 %)
	gastrointestinal tract	3 (25.0 %)
Defected genes	IFN-γR1	4 (33.3 %)
	IL-12 Rβ1	4 (33.3 %)
	NEMO	2 (16.7 %)
	TYK2	1 (8.3 %)
	STAT1	1 (8.3 %)
Treatment	antibiotics	12 (100.0 %)
	IFN-γ	8 (66.7 %)
	dexamethasone	2 (16.7 %)
	immunoglobulin	1 (8.3 %)
	surgery	2 (16.7 %)
Prognosis	good	8 (66.7 %)
	died	2 (16.7 %)
	poor	1 (8.3 %)
	unknown	1 (8.3 %)

avium, including one infected with *Mycobacterium gordonae*. One with *Mycobacterium asiaticum*, one with *Mycobacterium branderi*, one with *Mycobacterium chelonae* combined with *Mycobacterium gordonae*. Infected tissues were mainly lymph nodes (7/12, 58.3 %), bone/joint (5/12, 41.7 %), skin (5/12, 41.7 %), lungs (3/12, 25.0 %) and gastrointestinal tract (3/12, 25.0 %). In the 12 cases, four (33.3 %) had interferon γ receptor 1 (IFN-γR1) deficiency, four (33.3 %) had interleukin-12 receptor β1 (IL-12 Rβ1) deficiency, two (16.7 %) had NF-kappa B Essential Modulator (NEMO) deficiency, one (8.3 %) had TYK2 deficiency and one (8.3 %) had signal transducer and activator of transcription 1 (STAT1) deficiency. As for treatment, all patients used antibiotics. Four (33.3 %) used antibiotics only. Eight (66.7 %) were administered with IFN-γ, two (16.7 %) also took dexamethasone, our case was also placed on immunoglobulin in addition and two (16.7 %) underwent surgery. Eight (66.7 %) cases had a good prognosis, 2 (16.7 %) died (one was multidrug-resistant tuberculosis and another refused further treatment), one (8.3 %) had a poor prognosis without clearance of infection, and one (8.3 %) was unknown (Table 2). Some of the cases were evaluated for their immunological function, such as the level of IFN-γ production with phytohemagglutinin (PHA) stimulating peripheral blood mononuclear cell (PBMC). Sakai et al. [8] reported that their case produced less than 5.0 % IFN-γ compared with healthy subjects. In Schejbel et al.'s [12] study, the patient's IFN-γ level was less than 15.0 % compared to healthy controls.

5. Discussion

MSMD is an IEI due to molecular defects in the IL-12/IFN-γ-dependent signaling pathway. IL-12 and IFN-γ enhance the intracellular killing capabilities of macrophages, and IFN-γ is especially crucial in the resistance of mammalian hosts to pathogens, particularly bacteria and parasites which are capable of intramacrophage survival [19]. For patients with IFN-γR defects, the severity of the disease is inversely proportional to the residual level of IFN-γ, and some patients' defective genotype may never lead to the diseased phenotype [3,4]. While in IL-12 R defects, it is difficult to predict. The onset generally occurs in childhood but possibly in adulthood [1]. We have reported the first adult-onset MSMD patient in China. He presented with the infection at 18 years old. After nine years of repeated infections, he was finally diagnosed with MSMD with TYK2 deficiency. Unfortunately, further immunological functional testing was not performed after NGS because the patient refused. TYK2 is a member of the Janus Kinase (JAK) family of non-receptor tyrosine kinases. It plays a role in the signaling pathways for type I IFNs and various interleukins–6, 10, 12, 13, and 23 [2]. TYK2 deficiency was first reported in a 22-year-old Japanese male in 2006, who suffered from infections including BCG disease, non-typhoidal *Salmonella* gastroenteritis and hyper-immunoglobulin E (IgE) syndrome (HIES) [20]. Seven other cases from five unrelated families from Turkey,

Table 3
18MSMD-causing genes and 33 genetic etiologies [1,4,24,25].

Gene	Inheritance	Functional impairment
IL12RB1	AR	C
	AR	C
IL12B	AR	C
IL23R	AR	C
IL12RB2	AR	C
SPPL2A	AR	C
IRF8	AD	P
	AR	C
IFNGR1	AR	C
	AR	C
	AD	P
	AR	P
	AR	P
IFNGR2	AR	C
	AR	C
	AR	P
	AR	P
	AD	P
STAT1	AD	P
	AD	P
	AD	P
	AR	C
	AR	P
NEMO (*IKBKG*)	XR	P
CYBB	XR	P
TYK2	AR	P
	AR	C
JAK1	AR	P
RORC	AR	C
ISG15	AR	C
IFNG	AR	C
ZNFX1	AR	C
TBX21	AR	C

AD: autosomal dominant, AR: autosomal recessive, XR: X-linked recessive. C: complete, P: partial.

Morocco, Iran, and Argentina were reported in 2015 [21]. In 2016, an eight-year-old boy with Kurdish origin suffered from HIES was reported [22]. In 2018, two cases with partial TYK2 deficiency but not MSMD from one Japanese kindred were reported [23]. Among the eleven patients who had TYK2 deficiency, five showed the phenotype of MSMD.

According to the other eleven cases acquired from the literature review, the proportion of the two genders was similar in adult-onset MSMD patients. Most cases had disease onset during 18–30 years. The clinical presentations were nonspecific and varied, while the clinical course was mild. Up to date, 18 MSMD-causing genes and 33 genetic etiologies have been identified (Table 3) [1,4,24,25]. Including interferon gamma receptor 1 (*IFNGR1*), interferon gamma receptor 2 (*IFNGR2*), signal transducer and activator of transcription 1 (*STAT1*), *JAK1*, interferon regulatory factor 8 (*IRF8*), signal peptide peptidase-like protease 2 A (*SPPL2A*), interleukin-12 B (*IL12B*), interleukin-12 receptor B1 (*IL12RB1*), interleukin-12 receptor B2 (*IL12RB2*), interleukin-23 receptor (*IL23R*), interferon-stimulated gene 15 (*ISG15*), *TYK2*, RAR-related orphan receptor C (*RORC*), cytochrome B-245 Beta Chain (*CYBB*), *NEMO*, interferon gamma (*IFNG*), T-box transcription factor 21 (*TBX21*) and zinc finger nfx1-type containing 1 (*ZNFX1*) [25]. Different genes have different levels of allelic heterogeneity, resulting in several distinct disorders in their mode of inheritance, clinical penetrance, and protein expression level [26]. Pathogenic genes have diverse forms of mutations such as single-nucleotide variants (SNV), indels, duplications, insertions, and copy number variants (CNV) [27,28]. Nevertheless, these defective genes are physiologically highly homogenous. All the genetic abnormalities lead to deficiency in the production of and/or response to IFN-γ [4,7]. In all the MSMD patients, IL-12 Rβ1 deficiency, IFN-γR1 deficiency, and IL12B deficiency are dominant, which account for about 44.0 %, 17.0 %, and 12.0 %, respectively [24]. Noteworthy, *anti*–IFN–γ autoantibody-associated immunodeficiency is also recognized to constitute a late-onset, especially in adult-onset, 'autoimmune phenocopy' of MSMD.

The clinical manifestations of adulthood MSMD vary, involving multiple organs, and non-specific. Therefore, it is difficult to diagnose in the early stages. The case presented here had a diagnosis delay of nine years. Therefore, physicians should raise awareness of MSMD in clinical practice with the onset of adulthood. In addition, these MSMD cases were healthy until adulthood, implying that before disease onset, they had enough, though probably minimal, IFN-γ production required for protection against mycobacterial infection. In terms of the treatment, MSMD patients with inadequate IFN-γ could benefit from IFN-γ a lot. While in those without functional receptors for IFN-γ, hematopoietic stem cell transplantation (HSCT) seems to be the only curative option at present, though engraftment problems might appear [29]. Five MSMD-associated genes (*IFNGR1*, *IL12RB1, NEMO, TYK2, a*nd *STAT1)* have been found in adulthood onset patients currently. Mutations in *IL12RB1*, *NEMO*, and *TYK2* result in insufficient IFN-γ production, and though mutated *IFNGR1* and *STAT1* destroyed cellular response to IFN-γ, all the reported cases had partial deficiencies. This means theoretically, these patients could benefit much from a supplement of IFN-γ. In addition, once the pathogenic mycobacteria are found, infections could be well controlled with the appropriate antimycobacterial therapy. All the cases were treated with antibiotics, 8 with IFN-γ, in whom 2 also took dexamethasone. Though sometimes steroids can worsen NTM disease, we used 10 mg dexamethasone per day for only 5 days to improve our patient's condition, which was safe and supported by our clinical experience for over 10 years. We also used intravenous immune globulin [16] (10 g, qd × 7 days) for he was very weak at admission as well as the high disease burden implied by his condition. 66.7 % (8/12) patients had a good prognosis while 16.7 % (2/12) died. It is worth noting that one of the two deceased patients had multidrug-resistant tuberculosis with a deteriorated condition, which complicated the disease, and the other refused further treatment. Hence, antibiotics and IFN-γ should be administered to MSMD patients with adult-onset, which would refer them to good outcomes. For those with a heavy burden of disease, dexamethasone, and intravenous immune globulin may be effective options. However, more robust evidence is needed.

6. Conclusion

Adult-onset MSMD have complex clinical presentations and are difficult to recognize, which usually results in delayed diagnosis. Nevertheless, once diagnosed, antibiotics and IFN-γ might have good efficacy. When encountering adult patients with recurrent and refractory mycobacterial infections, especially in lymph nodes, bone/joint and skin, MSMD should be considered.

Ethical statement

Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article. And the study was reviewed and approved by the Ethics Committee of Shanghai Public Health Clinical Center (Reference Number: 2020-S150-01).

Funding

This study was supported by the grants from the Shanghai Public Health Clinical Center (KY-GW-2021-21), Shenzhen Fund for Guangdong Provincial High-level Clinical Key Specialties (SZGSP010), and grant from the Provincial Education Department for National Clinical Research Center for Infectious Disease (2020B1111170014).

Data availability statement

The research data (of our presented case) has not been deposited into a publicly available repository for privacy concern. But the data will be available on request to the corresponding author.

CRediT authorship contribution statement

Yang Yang: Formal analysis, Funding acquisition, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Lu Xia:** Formal analysis, Funding acquisition, Investigation, Methodology, Writing – review & editing. **Shuihua Lu:** Conceptualization, Funding acquisition, Writing – review & editing.

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.

Acknowledgement

Not available.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e22632.

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