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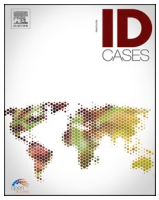

Case report

Anti-interferon-gamma autoantibody and salmonellosis: Case report and literature review

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ABSTRACT

Adult-onset immunodeficiency syndrome is characterized by the presence of anti-interferon-gamma (IFN-γ) autoantibody and the distribution of infections. Here, we describe *Salmonella enterica* bacteremia in a Thai woman who also had anti-IFN-γ autoantibody. The patient was also suffering from *Salmonella* osteomyelitis and a peri-orbital abscess. Her symptoms were completely eradicated after surgical intervention and the administration of appropriate antibiotics.

Introduction

Invasive non-typhoidal salmonellosis (iNTS) is a distinct clinical entity predominantly observed in patients with impaired immune function, especially T cell defects. Concurrently, adult-onset immune deficiency syndrome has been linked to an increased susceptibility to Salmonella infections, manifesting frequently as septicemia and disseminated non-tuberculous mycobacterial infections [1]. While skin and soft tissue involvement in salmonellosis is considered an uncommon presentation, this case highlights the presence of iNTS in a patient who initially presented with a skin and soft tissue infection. In addition, the presence of anti-IFN-γ autoantibody in this patient is an intriguing finding, highlighting the need for thorough investigations in cases of atypical clinical presentations.

Case presentation

A 66-year-old Thai woman presented with a two-centimeter-long, erythematous, excruciating mass on her right thigh. This lesion appeared six weeks before admission. A local hospital had provided the patient with outpatient care consisting of an incision, drainage, and a seven-day course of an unidentified oral antibiotic. However, the patient's symptoms persisted and worsened despite the medical intervention. She developed painful lumps on her right eyelid and left limb that progressed rapidly in the week leading up to her hospitalization. There was no history of persistent fever or weight loss in her past. The patient's medical history revealed well-controlled type 2 diabetes mellitus, with an HbA1c of 5.34 %. The patient's current medication regimen included 30 milligrams of pioglitazone per day. In addition, she had no history of owning pets, consuming uncooked food, engaging in high-risk sexual behavior, use of injectable drugs, or receiving tattoos. The patient denied any prior hospitalizations. The patient's physical examination revealed a body temperature of 36.3 degrees Celsius, a pulse rate of 90 beats per minute, a blood pressure of 104/54 mmHg, and a respiratory rate of 16 breaths per minute. A painful, erythematous, and warm mass-like lesion was observed on the patient's right eyelid, with no evidence of conjunctival injection (Fig. 1a). Due to the presence of this mass-like lesion, it was challenging to assess the right pupil and extraocular movement of the patient. On the right leg of the patient are two erythematous, warm, and excruciating lesions (Fig. 1b). Further physical examination revealed no indications of lymphadenopathy or hepatosplenomegaly. The remaining aspects of the physical examination were unremarkable. The complete blood count revealed a hemoglobin level of 6.5 g/dL, a white blood cell count of 25,030 cells/cu.mm, and a platelet level of 387,000 cells/cu.mm. There was a normal liver function present. *Salmonella enterica* was isolated from the blood culture. It was susceptible to amoxicillin-clavulanate (MIC = 8 μg/mL), ertapenem (MIC ≤ 0.5 μg/mL), imipenem (MIC ≤ 0.5 μg/mL), meropenem (MIC ≤ 0.5 μg/mL), piperacillin-tazobactam (MIC ≤ 8 μg/mL), and trimethoprim-sulfamethoxazole (MIC = 1 μg/mL) but resistant to ceftriaxone (MIC > 32 μg/mL), ciprofloxacin (MIC = 1 μg/mL) and levofloxacin (MIC = 2 μg/mL).

Contrast-enhanced computed tomography (CT) of the orbit was performed on the patient, revealing a 3.6 × 2.9 × 2.9 cm rim-enhancing

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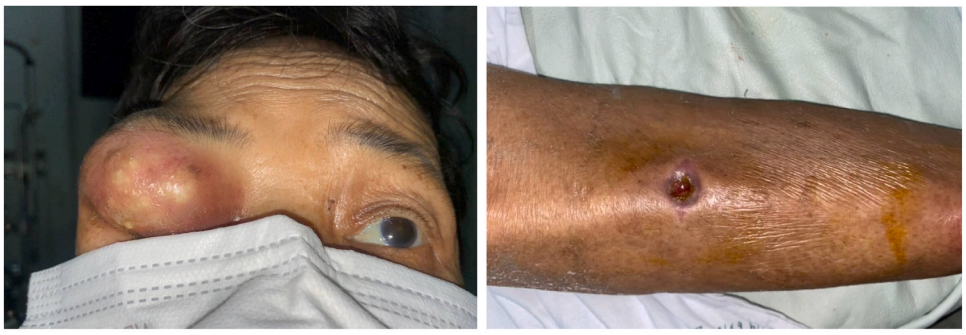

Fig. 1. Patient's Lesions at presentation (a) Right Eyelid (b) Right Leg.

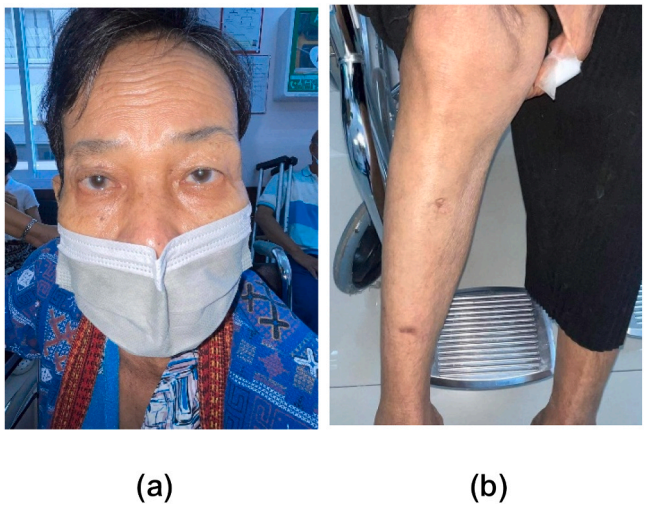

Fig. 2. Patient's progression after treatment (a) Right Eyelid (b) Right Leg.

lesion in the right supratemporal extraconal space. Moreover, the superior orbital rim exhibited evidence of bone degeneration. Based on these observations, it was suspected that the patient had an orbital abscess with osteomyelitis. The right eyelid was subsequently incised and drained, and a fluid culture revealed the presence of *Salmonella enterica*. The pattern of drug susceptibility of the pathogen observed in blood cultures was identical to that observed in the pus culture.

To ascertain the severity of the lesions, plain radiographs of both lower extremities were obtained. The conventional radiographs of both tibias revealed a region of osteomyelitis-like hypodensity. Magnetic resonance imaging (MRI) of both legs confirmed the diagnosis by revealing osteomyelitis in the right and left proximal and distal tibial shafts. In response to the MRI findings, the orthopedist performed debridement on both legs, and the pus culture revealed the same strain of *Salmonella enterica* found in the pus from the peri-orbital specimen and blood culture. iNTS was accompanied by peri-orbital abscess, orbital osteomyelitis, and abscesses and osteomyelitis in both extremities. Typically, patients with compromised cell-mediated immunity are diagnosed with iNTS. Therefore, a thorough assessment of the patient's cellular immune status was required. The HIV test for the fourth generation was negative. Nonetheless, plasma anti-IFN-γ autoantibody was positive. In this instance, adult-onset immunodeficiency syndrome with anti-IFN-γ autoantibody and iNTS is the definitive diagnosis for the patient. In addition to surgical intervention, the patient received intravenous meropenem at a dose of three grams per day, divided into three doses per day for two weeks, before a step-down to trimethoprim-sulfamethoxazole, an oral double-potency medication taken twice daily.

Two weeks after the patient's discharge, a follow-up examination revealed that the lesion had essentially vanished. The patient continued to receive oral antibiotics for a total of six weeks. Complete resolution of the lesion was observed after the antibiotic treatment, and the patient was discharged (Figs. 2a, 2b).

Discussion

Salmonellae are gram-negative bacteria of the Enterobacteriaceae family. This bacterial genus contains over 2500 distinct serotypes of *Salmonella*, which are classified based on the presence of specific antigens on the bacteria's surface [2]. Nontyphoidal *Salmonella* (NTS) refers to all *Salmonella* serotypes besides Typhi and Paratyphi A, B, and C. Typhoid fever, which *Salmonella* Typhi or Paratyphi can cause, and nontyphoidal fever, which several nontyphoidal *Salmonella* serovars can cause, are two distinct clinical syndromes that *Salmonella enterica* can cause [3]. iNTS is characterized by the presence of NTS bacteremia and focal extraintestinal infection. The most prevalent symptom of iNTS is primary bacteremia, which is characterized by fever, shivering, and sepsis syndrome [4]. In addition to osteomyelitis, meningitis, endovascular infections, and pneumonia, patients with iNTS may also exhibit focal infections [5].

Multiple risk factors for the development of iNTS have been identified. Among these are defects in type 2 interferon (IFN), mutations in the interleukin (IL)-12/IFN axis, acquired neutralizing autoantibodies to IFN-γ, defects in CD4 T cells, and the presence of certain medical conditions, such as advanced HIV disease, lymphoma, chemotherapy, corticosteroid use, and hemolytic anemia [5]. As observed in our patient, the presence of adult-onset immunodeficiency syndrome in conjunction with an anti-IFN-γ autoantibody is one of the identified risk factors for iNTS. Browne et al. coined the term "adult-onset immunodeficiency syndrome" to describe individuals with immune deficiency syndrome who displayed opportunistic infections and high-titer anti--IFN-γ neutralizing antibody [6]. In addition to tumor necrosis factor-alpha (TNF-α) and IFN-12, IFN-γ is necessary for controlling intracellular organisms, dimorphic fungi, and mycobacterial infections. IFN-γ is predominantly produced by CD4 and CD8 T cells, as well as natural killer cells, which are controlled by IL-12 and IL-18 [7]. The pathogenesis and precipitating factors of anti-IFN-γ autoantibody are unknown [8]. Several opportunistic infections have been linked to anti-IFN-γ autoantibody, the most prevalent being disseminated nontuberculous mycobacterial (NTM) infection. In addition, other opportunistic pathogens are prevalent, including *Talaromyces marneffei*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Burkholderia pseudomallei*, *Salmonella* species, and Varicella-zoster virus [9]. In this particular case report, we demonstrate the association between iNTS and adult-onset immunodeficiency syndrome, which is linked to anti-IFN-γ autoantibody.

The incidence of iNTS in patients with adult-onset immunodeficiency

Table 1
Adult-onset immunodeficiency Syndrome Associated with Anti-IFN-γ Autoantibody and iNTS.

Age at onset of disease/ Underlying disease	Presentation	Diagnosis	Co-infection	Treatment	Ref.
39-year-old woman/SLE on steroid	N/A	Recurrent *Salmonella* bacteremia, tubo-ovarian abscess	Disseminated *M. kansasii*	Ciprofloxacin	[10]
45-year-old man	Fever with skin lesions, progressive cough, and weight loss of 5 kg for 1 month	*Salmonella* bacteremia	Disseminated *M.abscessus* and *M.tuberculosis*	Ceftriaxone then oral trimethoprim-sulfamethoxazole	[11]
39-year-old man/ poliomyelitis	Fever, severe pain in both legs and multiple lymphadenopathies for 4 months	*Salmonella* bacteremia	Disseminated *M. abscessus M. Tuberculosis* osteomyelitis	Ciprofloxacin	[11]
50-year-old man	Acute fever with multiple pustules on both lower legs	*Salmonella* bacteremia	Disseminated *M.abscessus*	Levofloxacin	[12]

Abbreviations: SLE: Systemic lupus erythematosus; N/A: Not applicable

Table 2
iNTS Present with Skin and Soft Tissue Infection.

Age at onset of disease/ Underlying disease	Presentation	Diagnosis	Co-infection	Treatment	Ref.
51-year-old man/NHL	Low-grade fever and progressive pain in both thighs for 3 weeks	Osteomyelitis and pyomyositis	-	Ciprofloxacin	[13]
19 -year-old woman/SLE	Painful swelling in the right leg just below the knee with fever	Legs abscesses	-	Trimethoprim-sulfamethoxazole	[14]

Abbreviations: SLE: Systemic lupus erythematosus; NHL: Non-Hodgkin lymphoma

syndrome and anti-IFN-γ autoantibody is substantially higher in Asian countries than in the United States. Specifically, the incidence rate was estimated to be between 18 % and 19 % in Asian countries, whereas a report from the United States indicated a substantially lower incidence rate of 4 % [10].

A comprehensive analysis of relevant case reports reveals that patients with both adult-onset immunodeficiency syndrome and iNTS exhibit a consistent pattern. Specifically, these organisms manifest frequently in middle-aged patients with primary bacteremia, often in conjunction with NTM co-infection (Table 1) [11–13]. Consistent with these findings, our patient also manifested iNTS-related primary NTS bacteremia and osteomyelitis. Our case, however, deviated from the typical presentation in that it manifested disseminated cutaneous and soft tissue infection, a rare clinical feature.

Infections of the epidermis and soft tissues are uncommon in cases of iNTS, according to a comprehensive examination of relevant case reports. In the available literature, there are only two cases of patients diagnosed with non-Hodgkin lymphoma and systemic lupus erythematosus (SLE) (Table 2) [14,15]. Notably, none of these cases were associated with autoantibodies against IFN-γ. Notable is the fact that both cases exhibited a predominance of infection in the lower extremities, mirroring our patient's presentation. The presence of a peri-orbital abscess, however, distinguished our case from those previously reported. This is the first documented case of iNTS with an anti-IFN-γ autoantibody, demonstrating disseminated cutaneous and soft tissue infection and presenting with a peculiar peri-orbital abscess, to the best of our knowledge.

Antimicrobial susceptibility and the capacity to effectively penetrate infected tissues should guide the selection of antimicrobial therapy for the treatment of iNTS. Antimicrobial agents with favorable tissue penetration, such as quinolones and trimethoprim-sulfamethoxazole, are preferred in clinical practice [5]. Depending on the specific site of infection, the duration of antimicrobial treatment prescribed fluctuates. Standard guidelines recommend 7 to 14 days of oral or intravenous antibiotic treatment for systemic infections. Those with HIV and a CD4 cell count below 200 cells/mm3 were advised to take antibiotics for two to six weeks. Osteomyelitis and other focal infections are typically treated with antibiotics for four to six weeks [16]. In cases involving abscesses, surgical intervention may also be necessary. Due to its extended-spectrum beta-lactamase activity, carbapenem was administered as the initial treatment for our patient's *Salmonella* infection. Once the patient's clinical condition had improved and stability had been reached, oral trimethoprim-sulfamethoxazole was administered as a step-down therapy. Due to the length of time required to treat osteomyelitis, the total duration of antibiotic treatment was six weeks. In addition to antimicrobial therapy, surgical interventions, including incision and drainage procedures on the right peri-orbital abscess and debridement procedures on both lower extremities, were performed.

Salmonellosis with infection of the skin and soft tissues is a rare but conceivable manifestation of *Salmonella* infection, particularly in those with predisposing risk factors, such as adult-onset immunodeficiency syndrome associated with anti-IFN-γ autoantibody. The foregoing case illustrates the importance of considering immunodeficiency in patients with iNTS. This condition is typically treated with a combination of antimicrobial therapy and surgical intervention, depending on the severity of the infection. Clinicians must be vigilant in monitoring treatment response and evaluating potential complications, such as osteomyelitis, to ensure optimal patient care and outcomes. To reduce their risk of developing Salmonellosis, individuals with adult-onset immunodeficiency syndrome and an anti-IFN-γ autoantibody should avoid exposure to *Salmonella*-contaminated food and water. In addition, they should undergo routine monitoring and receive prompt medical care if they develop symptoms of infection, as early diagnosis and treatment are essential for a positive outcome.

Ethical approval

This study was reviewed by the Research Ethics Committee of the Faculty of Medicine, Chiang Mai University (study code: MED-2566-09530).

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CRediT authorship contribution statement

Saikhuan Towachiraporn: Data Curation, Writing - Original Draft, **Harit Thongwitokomarn:** Writing - Review & Editing, Supervision,

Parichat Salee: Conceptualization, Writing – Review & Editing, Supervision.

Declaration of Competing Interest

Authors declare no conflicts of Interests for this article.

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None.

Consent

The patient provided written consent for the publication of this case report and the inclusion of accompanying images. A copy of the written consent can be made available for review by the Editor-in-Chief of this journal upon request.

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