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Disseminated Nontyphoidal Salmonella Infection Mimicking Hemophagocytic Lymphohistiocytosis in a Previously Healthy Patient

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Abstract

Invasive nontyphoidal Salmonella (NTS) infection typically affects immunocompromised individuals but can rarely cause severe disseminated disease mimicking malignancy, autoimmune disorders, or hemophagocytic lymphohistiocytosis (HLH) in immunocompetent hosts.

A previously healthy 27-year-old man presented with prolonged fever, pancytopenia, hyperferritinemia, and hepatosplenomegaly, raising concern for HLH. Despite transient improvement with corticosteroids, he developed recurrent systemic inflammation, encephalopathy, pulmonary nodules with cavitary lesions, and progressive lymphadenopathy. Extensive infectious, autoimmune, and malignancy evaluations, including repeated blood cultures and plasma microbial cell-free DNA testing, were unrevealing. Ultimately, CT-guided retroperitoneal lymph node biopsy identified *Salmonella enterica* subsp. *enterica* through culture and 16S ribosomal RNA sequencing. Prolonged intravenous ceftriaxone therapy resulted in clinical and radiographic improvement.

Disseminated NTS infection can closely mimic HLH or malignancy, even in patients without known immunocompromising conditions. This case highlights the importance of tissue-based microbiologic diagnosis when noninvasive investigations are inconclusive, potentially preventing diagnostic delays and unnecessary immunosuppressive therapy.

Categories: Family/General Practice, Internal Medicine, Infectious Disease
Keywords: 16s ribosomal rna, hemophagocytic lymphohistiocytosis (hlh), immunocompetent adult, lymphadenopathy, salmonella enterica

Introduction

Nontyphoidal *Salmonella* (NTS) infections are a leading cause of foodborne illness and morbidity worldwide [1]. While the vast majority of NTS infections manifest as self-limiting gastroenteritis, invasive extraintestinal disease can occur. Classically, invasive NTS presents as bacteremia or focal metastatic infections-such as osteomyelitis, meningitis, or deep-tissue abscesses-predominantly in individuals with severe immunocompromising conditions, including HIV, malignancy, sickle cell disease, or advanced age [1].

Salmonella's ability to cause deep-seated, persistent infections stems from its complex pathophysiology. *Salmonella* species can survive and replicate intracellularly within host macrophages and reticuloendothelial tissues [2]. By hijacking macrophage vacuolar systems, the bacteria can establish a protective intracellular niche, evade humoral immunity, and form granulomatous reservoirs [2]. This intracellular persistence can fuel a chronic, dysregulated host immune response, leading to recurrent systemic dissemination and structural tissue destruction that can easily be mistaken for non-infectious inflammatory pathologies.

Although bacteremia is the hallmark of invasive NTS, atypical presentations are increasingly recognized as "great mimickers" in clinical practice. The resulting severe constitutional symptoms, diffuse lymphadenopathy, cytopenias, marked hyperferritinemia, and multi-organ involvement can intricately mirror lymphoma, systemic autoimmune conditions, or secondary hemophagocytic lymphohistiocytosis (HLH) [3].

Although invasive NTS infections have been reported in previously healthy individuals, deep-seated, lymph node-predominant disease remains exceptionally uncommon in patients without known immunocompromising conditions [4,5]. Unlike the more typical presentation of invasive NTS with detectable bacteremia or focal extraintestinal infection, predominantly lymphatic involvement without identifiable bloodstream infection presents a substantial diagnostic challenge. The ability of *Salmonella* to persist intracellularly within macrophages and reticuloendothelial tissues may contribute to localized infection with limited release of organisms or microbial DNA into the circulation. Consequently, blood cultures and plasma microbial cell-free DNA assays may remain negative despite ongoing invasive disease

[6,7]. This diagnostic limitation can delay recognition of the underlying infection, particularly when systemic inflammatory manifestations mimic HLH, lymphoma, or autoimmune disease, emphasizing the importance of tissue-based microbiologic evaluation.

We report a highly unusual case of recurrent, disseminated invasive nontyphoidal *Salmonella* (NTS) infection (specifically, *Salmonella enterica* subsp. *enterica*) in a previously healthy 27-year-old man. His clinical course was marked by a massive systemic inflammatory syndrome, progressive mediastinal and retroperitoneal lymphadenopathy, encephalopathy, and cavitary lung lesions. Initially, these findings mimicked HLH, malignancy, and systemic vasculitis, ultimately requiring a tissue-based molecular diagnosis.

Case Presentation

A previously healthy 27-year-old Hispanic man presented with a one-month history of persistent fevers, chills, drenching night sweats, generalized weakness, and unintentional weight loss. He denied tobacco use or alcohol abuse but reported a remote history of intravenous drug use a decade earlier and high-risk sexual behavior. Notably, he had traveled to Guatemala for a one-week family visit six weeks before symptom onset.

Upon admission, the patient was febrile at 101.7°F, tachycardic at 107 beats/min, and hemodynamically stable. Physical examination was notable for hepatosplenomegaly but without focal neurological deficits or distinct lymphadenopathy. Initial laboratory evaluation revealed profound pancytopenia and marked systemic inflammation (Table *1*).

Variable	Normal lab values	Admission
Hemoglobin (g/dL)	12.3 - 15.3 gm/dL	11.3
White blood cell (cells/μL)	4,500 - 11,000 cells/μL	2,500
Platelet ($x10^9$/L)	100,000 - 400,000/L	68,000
Ferritin (ng/mL)	21 - 247 ng/mL	2,312
C-Reactive Protein (mg/dL)	11 mg/dL	<1
Erythrocyte sedimentation rate (mm/hr)	0 - 15 mm/hr	38
Lactate dehydrogenase (U/L)	125 - 220 U/L	425
Aspartate transaminase (U/L)	6 - 31 U/L	51
Triglycerides mg/dL	7 - 149 mg/dL	238
Total serum bilirubin (mg/dL)	0.1 - 1.2 mg/dL	2
Soluble IL-2 receptor (pg/mL)	175 - 857 pg/mL	9,592 pg/mL
Interleukin-6 (pg/mL)	<2 pg/mL	17.7

TABLE 1: Initial laboratory values

Abbreviations: gm/dl = grams/deciliter, cells/μL = cells/microliter, U/L = units/liter, pg/mL = picograms/milliliter, mg/dL = milligrams/deciliter, and mm/hr = millimeters/hour.

A peripheral blood smear confirmed leukopenia and normocytic anemia without blasts or schistocytes.

An exhaustive infectious workup was initiated. Repeated peripheral blood cultures, a respiratory viral panel, HIV antigen/antibody testing, viral hepatitis serologies, syphilis screen, QuantiFERON-TB Gold assay, urinalysis, urine *Legionella* and pneumococcal antigens, and a nasal methicillin-resistant *Staphylococcus aureus* (MRSA) PCR were all negative. An autoimmune serologic panel was similarly unrevealing. Chest radiography and computed tomography (CT) of the chest and abdomen revealed diffuse bilateral pulmonary nodularity and marked splenomegaly (Figure *1* and Figure *2*).

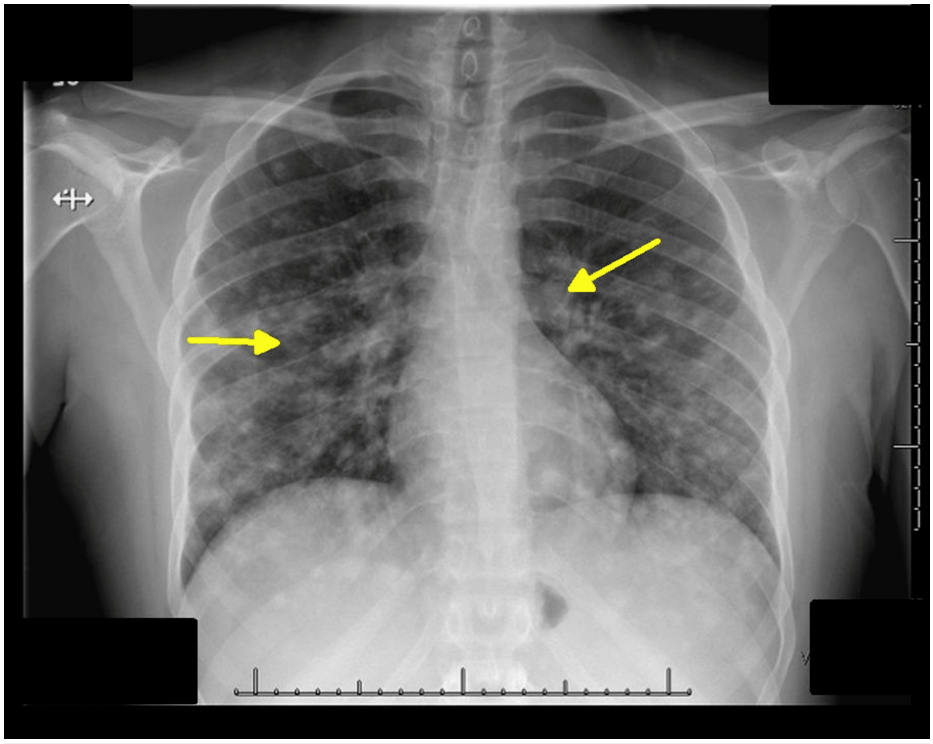


FIGURE 1: Chest radiography

Posteroanterior chest radiograph demonstrating diffuse, bilateral nodularity with scattered reticulonodular opacities throughout both lung fields (yellow arrows). Relative sparing of the extreme apices, with low concern for septic emboli.

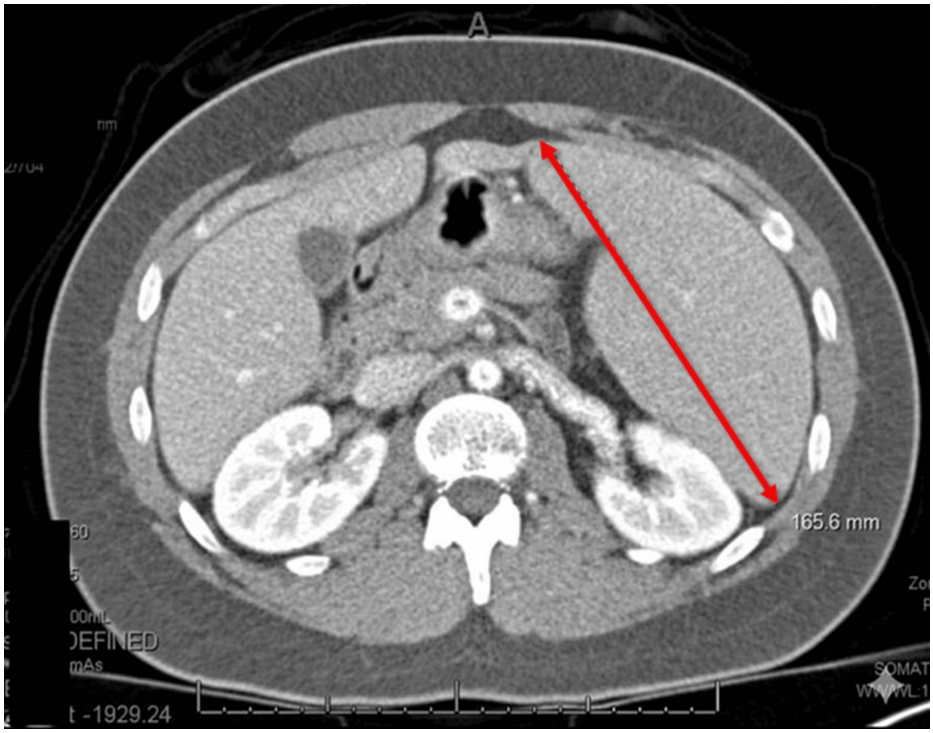


FIGURE 2: CT of the abdomen

Axial contrast-enhanced computed tomography scan of the abdomen demonstrating significant splenomegaly. The red arrow shows the spleen measuring 16.5 cm in its maximum dimension

Given the constellation of unremitting fevers, pancytopenia, hepatosplenomegaly, and marked systemic inflammation, hemophagocytic lymphohistiocytosis (HLH) was highly suspected. Laboratory evaluation demonstrated ferritin of 6,700 ng/mL, soluble interleukin-2 receptor (sIL-2R) of 20,000 pg/mL, fibrinogen of 132 mg/dL, and C-reactive protein of 11 mg/dL. A bone marrow biopsy did not show definitive hemophagocytosis. The previously calculated HScore was 188, corresponding to an estimated 70-80% probability of HLH [8]; this score should be verified against the complete laboratory dataset. High-dose intravenous corticosteroids led to rapid but transient clinical and laboratory improvement, and the patient was subsequently discharged.

One week after discharge, the patient returned with recurrent fevers, worsening cytopenias, and acute encephalopathy. Neurological examination revealed a fluctuating level of consciousness without focal deficits. Repeat CT imaging demonstrated progression of the numerous bilateral pulmonary nodules (Figure *3*), now highly concerning for septic emboli.

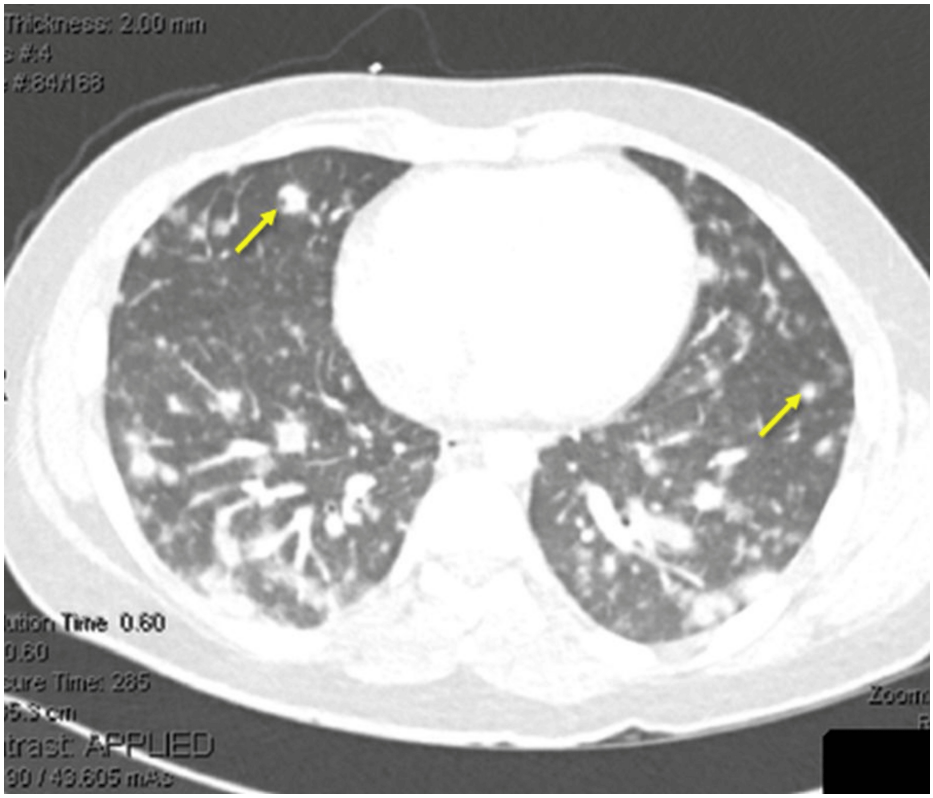


FIGURE 3: Repeat chest CT

Axial contrast-enhanced chest computed tomography scan showing multiple bilateral, ill-defined pulmonary nodules (yellow arrows) and ground-glass opacities.

To evaluate for an endovascular source, both transthoracic and transesophageal echocardiograms were performed, revealing no valvular vegetations or evidence of infective endocarditis.

Concurrently, serial blood cultures remained persistently negative. Empiric broad-spectrum antimicrobial therapy with vancomycin and cefepime was initiated and later de-escalated to cefepime monotherapy, administered at 2 g (grams) intravenously every 8 hours for 7 days. A diagnostic bronchoscopy with endobronchial ultrasound-guided lymph node sampling was performed, which excluded malignancy but yielded negative cytologic and microbiologic stains. Although partial clinical stabilization was achieved, the intended antimicrobial course was truncated when the patient left against medical advice before a definitive diagnosis could be established.

Three weeks later, the patient presented for a third time in extremis, with high fevers, hypotension, severe encephalopathy, and profound constitutional wasting. A diagnostic lumbar puncture was performed; cerebrospinal fluid analysis and cultures were unrevealing. Repeat CT imaging of the chest, abdomen, and pelvis demonstrated progressive, bulky mediastinal and retroperitoneal lymphadenopathy (Figure *4*) suspicious for lymphoma, along with newly developed cavitary changes in the right middle lobe and in pulmonary lesions of the left upper lobe (Figure *5*).



FIGURE 4: Repeat CT of abdomen

Axial contrast-enhanced computed tomography scan. The yellow arrows highlight a well-defined, enlarged retroperitoneum/peripancreatic lymph node measuring 17.3 mm in short-axis diameter, located anterior to the abdominal aorta.

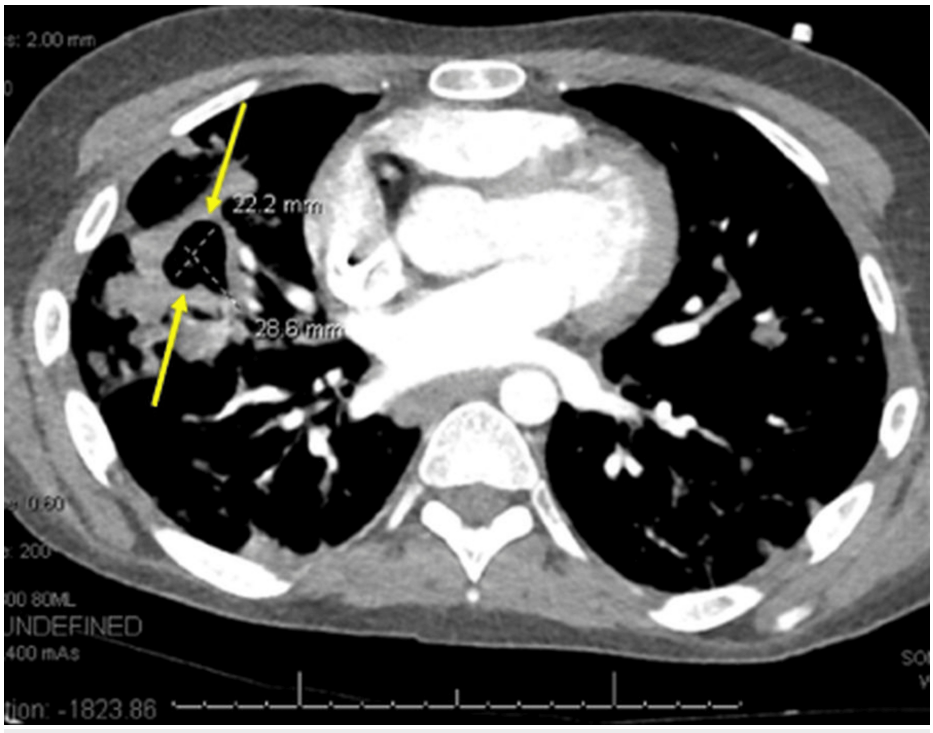


FIGURE 5: CT of the chest

Axial contrast-enhanced computed tomography scan of the chest demonstrates a thick-walled de novo cavitary mass (yellow arrows) located within the right lung parenchyma. Bidirectional caliper measurements demonstrate a lesion measuring approximately 22.2 mm by 28.6 mm. Central necrosis or air-fluid collection is visible within the center of the cavitation, surrounded by irregular, consolidative soft tissue borders.

Given recurrent systemic illness following a prematurely discontinued antimicrobial course, a tissue-based

diagnostic strategy was pursued. The patient underwent a CT-guided core needle biopsy of an enlarged retroperitoneal lymph node. Histopathological evaluation excluded lymphoma and metastatic malignancy. Despite a negative concurrent plasma microbial cell-free DNA (mcfDNA) assay, retroperitoneal lymph node tissue culture and 16S ribosomal RNA (rRNA) sequencing identified *Salmonella enterica* subsp. *enterica*. Antimicrobial susceptibility testing demonstrated susceptibility to third- and fourth-generation cephalosporins.

The patient was transitioned to a prolonged course of targeted intravenous ceftriaxone therapy.

This directed regimen resulted in the complete resolution of his pyrexia, rapid neurological clearing, and a gradual hematologic recovery. Follow-up radiographic imaging documented the near-complete regression of both the systemic lymphadenopathy and the cavitary pulmonary lesions.

Discussion

Most nontyphoidal *Salmonella* (NTS) infections present as self-limited gastroenteritis, but about 3% to 8% progress to bacteremia and invasive extraintestinal disease [9]. Although adults with severe immunosuppression are the highest-risk population, serious and invasive infections also occur in immunocompetent individuals [10]. In this patient, *Salmonella enterica* subsp. *enterica* exhibited several unusual clinical manifestations that substantially complicated the diagnostic evaluation, closely mimicking multiple non-infectious inflammatory and malignant pathologies [11].

The patient's initial constellation of pancytopenia, marked hyperferritinemia, elevated soluble interleukin-2 receptor (sIL-2R) levels, splenomegaly, and persistent pyrexia strongly suggested secondary hemophagocytic lymphohistiocytosis (HLH). Although the calculated HScore indicated a high probability of HLH, a bone marrow examination failed to demonstrate definitive hemophagocytosis. Secondary HLH triggered by severe bacterial pathogens is increasingly recognized [12,13], and disseminated *Salmonella* infection is a rare but critical precipitating factor. A 2023 *Chest* case report described similar findings, detailing a patient with disseminated *Salmonella* whose clinical presentation of severe systemic inflammatory response syndrome (SIRS), hepatosplenomegaly, and profound hyperferritinemia was initially indistinguishable from sepsis and largely masked an underlying secondary HLH phenotype [14]. However, a fundamental distinction sets our case apart and underscores its diagnostic complexity. The 2023 case involved overt, focal bone invasion due to emphysematous osteomyelitis [14]. Our patient's infection was predominantly associated with deep mediastinal and retroperitoneal lymphadenopathy, alongside pulmonary lesions. A potentially compartmentalized infection may explain why repeated blood cultures and plasma microbial cell-free DNA testing were negative despite ongoing systemic inflammation; the mechanism of encephalopathy remains uncertain.

Diagnostic uncertainty is common in adult hemophagocytic syndromes, where systemic inflammatory biomarkers alone cannot reliably distinguish primary immune dysregulation from infection-driven hyperinflammation [15]. This diagnostic dilemma was further compounded by the patient's transient clinical improvement after corticosteroid administration, which masked the active infection and delayed identification of the underlying bacterial source [16].

In addition to HLH mimicry, the development of progressive mediastinal and retroperitoneal lymphadenopathy, accompanied by profound constitutional symptoms, raised a strong diagnostic concern for lymphoma. Although previous reports have described invasive *Salmonella* infections presenting as typhoid-like syndromes [4] with prolonged constitutional symptoms in immunocompetent adults, *Salmonella*-associated lymphadenitis is a notorious radiographic mimic of malignant disease that requires histopathological confirmation [17]. The initial bronchoscopic lymph node sampling in our patient was nondiagnostic, underscoring the high likelihood of sampling error in deep-seated nodes and emphasizing the vital clinical importance of obtaining core tissue biopsies from sites demonstrating progressive radiographic involvement.

Furthermore, the patient experienced recurrent episodes of encephalopathy without focal neurological deficits or cerebrospinal fluid (CSF) abnormalities. Neurological manifestations of invasive salmonellosis are uncommon but well documented, including encephalopathy, meningitis, cerebral abscesses, and altered mental status driven by severe systemic inflammatory responses [18]. Although the patient's CSF analysis remained negative, a profound systemic cytokine storm likely contributed to the altered neurocognitive status.

The recurrent clinical course may have reflected incomplete antimicrobial therapy after discharge against medical advice, together with persistent deep-seated infection. The isolated *Salmonella* was susceptible to third- and fourth-generation cephalosporins, arguing against documented cephalosporin resistance as the explanation for recurrence. *Salmonella* can persist within macrophages and reticuloendothelial tissues [19], but intracellular sequestration as the specific mechanism of recurrence cannot be established in this patient.

This case also highlights the limitations of traditional bloodstream-based diagnostic modalities in localized

or compartmentalized infections. Repeated blood cultures remained persistently negative despite extensive, multi-organ disease. Concurrent plasma microbial cell-free DNA (mcfDNA) testing was negative, whereas localized tissue culture and 16S ribosomal RNA (rRNA) sequencing of the retroperitoneal node ultimately established the definitive diagnosis. Although plasma mcfDNA assays show promising sensitivity in generalized invasive infections, their diagnostic yield decreases dramatically when the pathogen burden in the bloodstream is low or strictly compartmentalized. Consequently, negative blood cultures and noninvasive molecular assays must not preclude an aggressive tissue-based diagnosis when suspicion for an occult infection remains high [6,7].

Current therapeutic recommendations for invasive NTS infections call for third-generation cephalosporins, with prolonged treatment reserved for focal metastatic disease. The duration of therapy for focal invasive infection should be individualized according to the involved sites, clinical response, and susceptibility findings, with appropriate clinical and radiographic follow-up. Although HIV testing was negative and no immunocompromising condition was known, anti-interferon-gamma autoantibody and complement deficiency testing were not performed; an occult immune defect therefore cannot be fully excluded.

Conclusions

Disseminated *Salmonella enterica* subsp. *enterica* infection can mimic secondary hemophagocytic lymphohistiocytosis (HLH), lymphoma, autoimmune disease, and septic embolic phenomena, even in a patient without a known immunocompromising condition. Persistently negative blood cultures and plasma microbial cell-free DNA testing do not exclude deep-seated bacterial infection. In this case, retroperitoneal lymph node culture and 16S ribosomal RNA sequencing established the diagnosis and enabled targeted antimicrobial therapy. Tissue-based microbiologic evaluation should be considered when unexplained systemic inflammation and progressive focal abnormalities persist despite unrevealing noninvasive testing. Identifying an infectious trigger is particularly important before escalating immunosuppression in patients with HLH-like presentations.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Steve Carlan, Sara Ubosy, Mustafa Nuaimi, Mario Madruga

Drafting of the manuscript: Steve Carlan, Sara Ubosy, Ali Alrubaye

Critical review of the manuscript for important intellectual content: Steve Carlan, Mustafa Nuaimi, Mario Madruga

Acquisition, analysis, or interpretation of data: Sara Ubosy, Ali Alrubaye

Supervision: Mario Madruga

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **AI use statement:** The authors have declared that no AI tools were used during the work or in the drafting of this article. The authors take full responsibility for the work. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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