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Diagnostic Dilemma in a Patient With Chronic Fistulating Nonhealing Ulcer

Sedigheh Rafiei Tabatabaei [1], Abdollah Karimi [1], Ali Amanati [1,*], Maryam Kazemi Aghdam [2], Bibi Shahin Shamsian [3], Javad Ghoroubi [4]

[1]Pediatric Infections Research Center, Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran
[2]Pediatric Pathology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran
[3]Pediatric Congenital Hematologic Disorders Research Center, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran
[4]Pediatric Surgery Research Center, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran

*Corresponding author: Ali Amanati, Pediatric Infections Research Center, Department of Pediatric Infectious Diseases, Mofid Children's Hospital, Dr. Shariati Ave., P.O.BOX: 1546815514, Tehran, IR Iran. Tel/Fax: +98-2122226941, E-mail: ali_amanati_1356@yahoo.com.

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Here, we report on a ten-year-old girl with chronic draining nonhealing ulcer in her neck and unilateral cervical chronic lymphadenopathy. Her ulcer had poor clinical response to broad spectrum antibiotics and anti-tuberculosis treatment. She had undergone several wound biopsies with no conclusive results. She was otherwise healthy with no known underlying disease. Final wound excisional biopsy with specific immunohistochemistry (IHC) staining confirmed her diagnosis. Histopathology report and IHC were compatible, indicating an anaplastic large cell lymphoma.

Keywords: Wounds and Injuries; Neck; Lymphatic Diseases; Lymphoma, Large-Cell, Anaplastic

1. Introduction

A chronic nonhealing wound is described as a wound failing to heal within three months and it is extremely complex to manage and diagnose contributing factors of poor healing (1, 2). Complications of these wounds are risk of severe pain, septicemia, hospitalization, and in some cases severe morbidity. Exact identification of pathogenic organisms in chronic wounds is difficult and varies depending on the modes of sampling and the diagnostic methods (culturing or molecular methods). The most common bacteriological dilemma in chronic wounds is differentiation between nonpathogenic colonization and other pathogenic organisms. The most common bacterial isolates on wounds are *Staphylococcus aureus*, coagulase-negative staphylococci, *Enterococcus faecalis*, *Proteus* species, anaerobic bacteria, and *Pseudomonas aeruginosa*, yet other significant pathogens such as *tuberculosis*, atypical *mycobcteria*, *nocardiosis*, *actinomycosis* and fungal infection should always be considered. On the other hand, when chronic nonhealing wounds are difficult to treat with antibiotics, consideration of biofilm formation, which necessitates overcoming increased minimal inhibitory concentrations (MICs) of biofilm growing organisms such as *Pseudomonas aeruginosa,* is warranted (3, 4). Another significant issue in managing these wounds is investigation of the underlying predisposing factors contributing to failure in wound healing such as ischemia, venous insufficiency, diabetes, neuropathy, malnutrition, corticosteroids therapy, vasculitis, immune suppression and malignancy (2, 5).

2. Case Report

A ten-year-old girl was admitted to our center with a chronic fistulating nonhealing wound. In the initial physical examination she had a large (about 5 × 7 centimeters) draining deep ulcer in the anterior cervical triangle below her right mandible and surrounded swelling. As her mother notified, she had a unilateral neck swelling since three months ago. She had been hospitalized 2 times before admission to our ward. The neck sonography performed in the primary center revealed unilateral multiple lymph nodes on the right side. She was put on anti-tuberculosis treatment after discovery of acid-fast bacilli (AFB) in the lymph nodes fine needle aspiration in her first admission to that center. She stopped her medications after about 3 weeks and was admitted to another center for excisional lymph nodes biopsy because of poor clinical improvement after the primary treatment. In first pathology report only necrosis with inflammation without evidence of tuberculosis were noted. She was also examined for bone marrow aspiration which revealed no evidence of malignancy and tuberculosis. Finally, because of no remarkable change in her neck swelling and draining wound despite previous treatment, she

Implication for health policy/practice/research/medical education:
We hoped to emphasize to all clinicians that close follow up of chronic disease is an important part of accurate management. Attention to any possible underlying cause, which could contribute to poor clinical response, should always be kept in mind. As in our case repeated biopsy may be needed to attain diagnosis.

was referred to our hospital. In the first evaluation she had a large deep ulcer on the right side of her neck with purulent discharge, which was accompanied by a unilateral neck swelling. She had no hepatosplenomegaly or any noticeable intra-abdominal lymphadenopathy. In her clinical evaluation and vital sign chart, intermittent pattern of low-grade fever was noted. According to previous positive reports of AFB in lymph node fine needle aspiration we start to investigate tuberculosis in the patient. Complete blood count (CBC) revealed WBC: 51700/μL, neutrophil: 92%, lymphocyte: 3% and HB: 8.3 g/dL, MCV: 75.8 fL and platelet count 521000/μL. Acute phase reactants were significantly high (erythrocyte sedimentation rate [ESR] = 80, C-reactive protein [CRP] = 102). Blood culture had negative results. Liver transaminases and bilirubin were also in normal limits. In the initial work up for tuberculosis three times gastric washing for AFB staining, culture and polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* all had negative results. Tuberculin skin testing (TST) was also performed. TST and chest X-ray (CXR) were also done for her parents. Her father had purified protein derivative (PPD) injection induration of about 28 millimeters after 48 hours but TST of the patient and her mother had negative results. She had no known exposure to tuberculosis. In CXR, only soft tissue in the right part of the neck was prominent and there was no evidence of active paranchymal involvement or hilar adenopathy. Sonography of the neck revealed evidence of subcutaneous edema along with distorted structure and echotexture in the right side of the neck and multiple enlarged lymph nodes in both sides of the neck with areas of necrosis. Spiral computerised tomography (CT) scan of the neck showed bilateral lymphadenopathies, predominant on the right side (Figure 1). Abdominopelvic spiral CT scan with intravenous (IV) contrast media showed a hypodense lesion measuring 25 × 17 mm in the inferomedial aspect of the spleen (Figure 2). Wound debridement and drainage for microbiological evaluation was performed by a surgeon in the operating room. Copious pus material was drained and sent for gram, AFB stain, aerobic and anaerobic culture and cytology, where results were negative for *Mycobacterial tuberculosis* PCR, AFB staining, fungal element and aerobic culture. Cytology also did not reveal any evidence of malignant cells. Due to previous positive AFB results for tuberculosis from wound smear and clinical similarity to scrofula, despite no further evidence of tuberculosis, anti-tuberculosis treatment with four-drug initial regimen (isoniazid, rifampicin, pyrazinamide and ethambutol), which had been started previously, was continued. With the suspicion of nocardiosis, imipenem was also added. The patient was again admitted about 3 weeks later with fever and increased wound drainage with a bad smell. Once more, she had leukocytosis. In the second admission, left cervical adenopathy was noted and in the left axillary ultrasonography two lobulated hyperoechoic lesions were seen in favor of conglomerated lymph nodes. Because of these new findings and progressive enlargement of right cervical nodes, initial workup for immunodeficiency was also performed. Cellular chemotaxis was normal. Immunoglobulin profile revealed serum immunoglobulin E (IgE) of > 400 IU/mL and serum Immunoglobulin A (IgA) of 385 IU/mL (normal up to 115). Immunoglobulin G (IgG) and immunoglobulin M (IgM) were in normal limits of age. In further evaluation, human immunodeficiency virus (HIV) antibody by enzyme-linked immunosorbent assay (ELISA) was negative, which examined twice. The nitroblue-tetrazolium (NBT) test was in normal range. Perinuclear anti-neutrophil cytoplasmic antibody (PANCA), cytoplasmic antineutrophil cytoplasmic antibody (CANCA), antinuclear antibody (ANA) and anti ds-Deoxyribonucleic acid (DNA) were negative and Total complement activity (CH50) was also within normal limits.

Wounds gradually got better and wound secretions decreased. She was afebrile for about 2 weeks and then she was again afebrile. Due to no definite diagnosis and multifocal reticuloendothelial system involvement (spleen and bilateral cervical adenopathy), she was once again planned for wound debridement and lymph node biopsy. Only necrotic tissue and chronic inflammation was noted in the repeated biopsy. The smear again checked for AFB, nocardiosis, actinomycosis, fungal element potassium hydroxide preparation (KOH) and cytology for malignancy where all had negative results. She was discharged after defeverness with regular visits and close follow up. The third admission was followed by fever and no significant improvement in her ulcers. She had 2 peaks of high-grade fever (up to 40°C), daily for a week in the initial days, after the third admission. However, her fever declined and she became afebrile from that point onwards for about 2 weeks, and again became febrile with a similar pattern as previous, with a low peak (less than 38.5°C).

All cultures including blood, urine and wound had negative results in the third admission. It is important to note that she had a constant leukocytosis with polymorphonuclear cell (PMN) predominance in serial CBC count, which was accompanied by high ESR and CRP. The result of bone marrow aspiration (BMA) and flow cytometry were normal. In the absence of evidence for bacterial, fungal or other infections and suspicion for underlying diseases, we decided to take another lymph node biopsy and sent the tissue specimen for more specific molecular evaluation. In the histopathological study of the final biopsy, large scattered atypical cells were seen, where some had multinucleated or binucleated prominent nucleoli, little cytoplasm and Reed–Sternberg-like features. In the primary IHC study, only CD5 and ALK were weakly positive in a few atypical cells and CD30 was also positive in atypical cells. Pathological blocks were sent

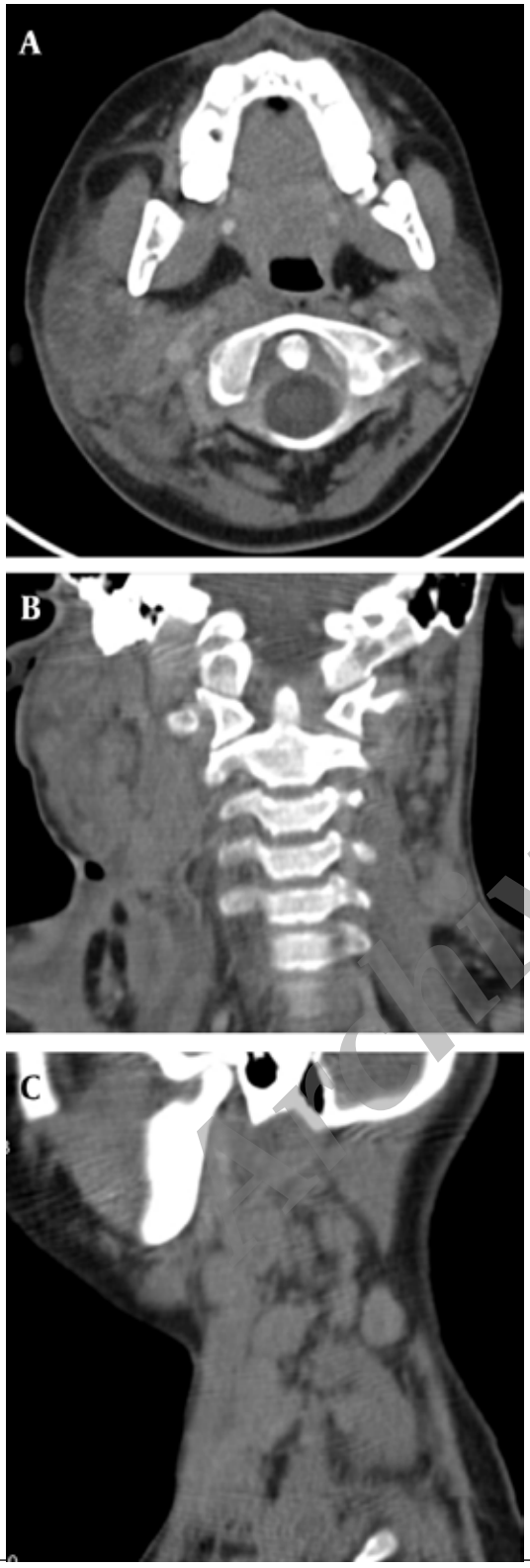

Figure 1. Bilateral Lymphadenopathies Predominant on the Right Side of the Cervical Region

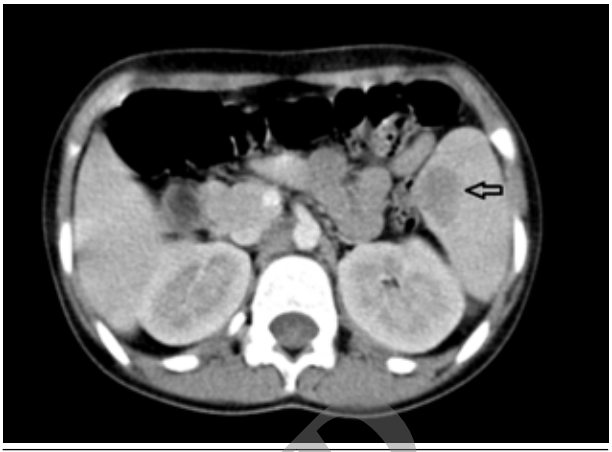

Figure 2. A Hypodense Lesion in Inferomedial Aspect of the Spleen

to another center for review and further evaluation. Last IHC revealed positive immunoreactions with CD30, CD5, Bcl-2 and clusterin in large cells. No immunoreaction with CD20, CD3, CD45, CD15, ALK, P53, S100 and EMA was detected. Ki-67 immunoreaction was more than 50% in the neoplastic cells. These findings were compatible with anaplastic lymphoma. After confirmation of the diagnosis, the patient was referred to the hematology-oncology ward for treatment.

3. Discussion

Although chronic lymphadenopathy is familiar to pediatricians, chronic fistulating lymphadenopathy is less common and occasionally becomes a diagnostic problem. After demonstration of lymphadenopathy in a patient, step by step approach should be used to attain accurate diagnosis. These include history taking (time of initial symptoms, duration, associated signs and symptoms, history of animal exposure, traveling and drug history), physical examination (including, any other site of reticuloendothelial system involvement), early and late work up (5-8). In contrast to acute onset suppurative cervical lymphadenitis, which is caused mostly by *Staphylococcus aureus* or *Streptococcus pyogenes*, etiological causes of chronic suppurative lymphadenopathy are different (9, 10). Common infectious causes of cervical lymphadenopathy include *Mycobacterium tuberculosis*, none tuberculosis mycobacteria, cat scratch disease, toxoplasmosis and infectious mononucleosis. Other etiological causes could be categorized in to neoplastic, autoimmune (Kawasaki disease) (11), auto-inflammatory [periodic fever with aphthous stomatitis phayngitis and adenitis (PFAPA) syndrome] and idiopathic diseases (Kikuchi-Fujimoto disease) (12, 13). Among these, nearly all of the infectious causes (except of viral causes) could be suppurative. Suppuration was also seen in some of the neoplasms (Hodgkin disease and non-Hodgkin disease

including anaplastic large cell lymphoma and metastatic carcinoma) (14-16).

Only rarely, autoimmune diseases may be accompanied by suppuration. Suppuration is a non-typical finding in other causes such as Kikuchi disease. In this case, our initial step was to take the patient's history again for any exposure to endemic infectious diseases, which cause chronic lymphadenopathy (e.g. tuberculosis). Additionally, we reviewed her first bone marrow smears in addition to pathology block of the first lymph node biopsy. Tuberculosis, atypical mycobacterial infections, toxoplasmosis, infectious mononucleosis (PCR in tissue biopsy in addition to serology for *Epstein–Barr virus* (EBV) was investigated, which had negative results. Cat scratch disease was not examined because of limited availability to serology and PCR assay for detection of *Bartonella henselae*. In the four wound biopsies we did not find any evidence of malignancy or infection pathogens. Due to persistent fever, hypodense splenic lesion, poor clinical response to broad-spectrum antibiotics and full six-month course of anti-tuberculosis treatment in addition to high acute phase reactants, we continued to investigate any underlying immunodeficiency and further examined for malignancy by histopathology and immunohistochemistry staining of the wound. Consequently, initial work for primary and secondary immunodeficiency was done and finally, the patient was planned for a wound biopsy. Early immunological evaluation revealed no evidence of any primary and secondary immunodeficiency. This difficult case had a wide variety of differential diagnosis including chronic lymphadenopathy with an infectious cause as well as Hodgkin and non-Hodgkin lymphoma including anaplastic large cell lymphoma. Anaplastic large cell lymphoma (ALCL) is a rare disease in children accounting for 10 to 15% of all childhood non-Hodgkin lymphomas. ALCL is characterized by the proliferation of large pleomorphic cells of a T/null phenotype that tend to invade the lymph node sinuses and express the CD30 antigen. In children, most ALCLs exhibit (2:5) translocation, which can be detected by anaplastic lymphoma kinase (ALK) antibodies. ALK-positive (ALK+) ALCL is usually a systemic disease that frequently involves extra-nodal sites. In children, 18-25% of systemic ALCLs develop skin manifestations during the course of the disease and this is a poor prognostic factor. Systemic ALK-negative (ALK) ALCL is included in the updated World Health Organization (WHO) classification as a separate preliminary entity. ALK-negative ALCL accounts for less than 5% of pediatric systemic ALCLs. However, both ALK-positive and ALK-negative ALCLs are considered potentially disseminated diseases. Primary cutaneous ALCL (cALCL) is regarded by the WHO as a separate disease entity and belongs to the spectrum of cALCLs; remains confined to the skin, virtually never disseminates beyond local lymph nodes, and shows an excellent prognosis after surgical resection without systemic therapy. Our patient, based of cervical lymph nodes and spleen involvement, was classified as systemic ALCL (ALK negative) (14, 16). The peak incidence of ALK-negative ALCLs is in adults (40-65 years) unlike ALCL, ALK+ which occurs mostly in children and young adults. It is important to note, our case was much younger at presentation. ALK-negative ALCLs typically involve the lymph nodes, with extranodal disease being less prevalent than that found in ALK+ cases. The most common sites of extranodal involvement are the skin, bone and soft tissues, as in our case (17).

Close follow up and search for the underlying cause of chronic suppurative lymphadenopathy is necessary. Extensive work for lymphoid malignancies, including bone marrow aspiration, bone marrow biopsy, immunophenotypic analysis lymph node histopathology and immunohistochemical studies should be considered. Early or extensive diagnostic immunological work is mandatory for these patients, based on associated signs and symptoms, age and superimposed infectious agents. Finally, we emphasize to that one time biopsy may not reveal coetaneous malignant lymphomas such as this case and these entities should be kept in mind for any unresolved and unexplained chronic fistulating lymphadenopathies.

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Authors' Contribution

All the authors contributed in writing this article.

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