Respiratory Medicine Case Reports 5 (2012) 42–44

Contents lists available at SciVerse ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

Case report

Are all granulomatous lesions tuberculosis?

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ARTICLE INFO

Article history:
Received 20 September 2011
Accepted 4 October 2011

Keywords:
Granulomatous lesions
Causes
Tuberculosis

ABSTRACT

Introduction: Granulomatous reactions are seen in a wide variety of diseases.
Methods: We present 3 cases referred to our clinic with presumptive diagnosis of tuberculosis (TB) were diagnosed as nontuberculous granulomatous diseases.
Results: Three cases were diagnosed as Tularemia, Cat-Scratch Disease (CSD) and idiopathic granulomatous mastitis (IGM) respectively.
Conclusion: In countries with high incidence of TB, TB is considered firstly in differential diagnosis of granulomatous diseases. Detailed anamnesis and physical examinations should be done in differential diagnosis of granulomatous diseases, and TB must be excluded.

1. Introduction

Granulomatous reactions are seen in a wide variety of diseases as infectious diseases, sarcoidosis, crohn disease, wegener granulomatosis, romatoid artritis, berilyosis, drug reactions, foreign body aspiration. We present 3 cases referred to our clinic with presumptive diagnosis of tuberculosis (TB) were diagnosed as nontuberculous granulomatous diseases.

2. Case 1

A 63-year-male patient had right axillary lymphadenopathy (LAP) measuring 20 mm in diameter. LAP biopsy was reported as suppurative granulomatous lymphadenitis. He was referred to our clinic with presumptive diagnosis of TB. With detailed anamnesis we learned that LAP was developed 1 month after thorn prick right hand index finger. Chest radiography was normal (Fig. 1). PPD was 10 mm. Sputum smears Acid Fast Bacilli (AFB) and TB cultures were negative for five times. Erithrocyte sedimentation rate (ESR) was 16 mm/h. Serum ACE, calcium and urinary calcium levels were within normal range. All other laboratory findings were normal. Abdominal and neck Ultrasonography (US) examinations were normal. Because of history of thorn prick, Francisella tularensis agglutination test was performed by presumptive diagnosis of Tularemia and it was reported as 1/1280 positive. Treatment with Streptomycin and Doxycycline was started.

3. Case 2

A 25-year-old male patient admitted to a clinic with a complaint of left axillary swelling. US revealed left axillary LAP measuring 27 × 12 mm in size. Axillary LAP biopsy was reported as necrotizing granulomatous lymphadenitis. He was referred to our clinic with presumptive diagnosis of TB. Chest radiography was normal (Fig. 2). ESR was 12 mm/h. Serum ACE, calcium and urinary calcium levels were within normal range. All other laboratory findings were normal. PPD was 12 mm. Three sputum smears AFB and TB cultures were negative. Neck US yealded bilateral cervical lymphadenopathy largest measuring 6 × 13 mm in size. Detailed anamnesis was obtained from patient, it was learned that he had a history of cat bite on left hand middle finger 1 month ago. We saw skin lesion at the contact site. LAP biopsy specimens reevaluated by pathologist. It was reported as micro abscess and necrotizing granulomatous lymphadenitis. He was diagnosed as Cat-Scratch Disease (CSD) and treatment with Doxycycline was started.

4. Case 3

A 40-year-old female without any complaint admitted to a general surgery clinic for routine clinical breast examination. She had no history of childbirth, nursing, oral contraceptive use, hyperprolactinemia within 2 years. Breast US showed punctate microcalcification in left upper-middle zone and mammography showed nodulary density in left middle zone. Excisional biopsy of breast tissue revealed noncaseating lobular granulomas composed of epithelioid histiocytes and multinuclear giant cells and intraductal papilloma, with no evidence of malignancy. She was referred to our clinic with presumptive diagnosis of TB. Tissue sample was

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doi:10.1016/j.rmedc.2011.10.001

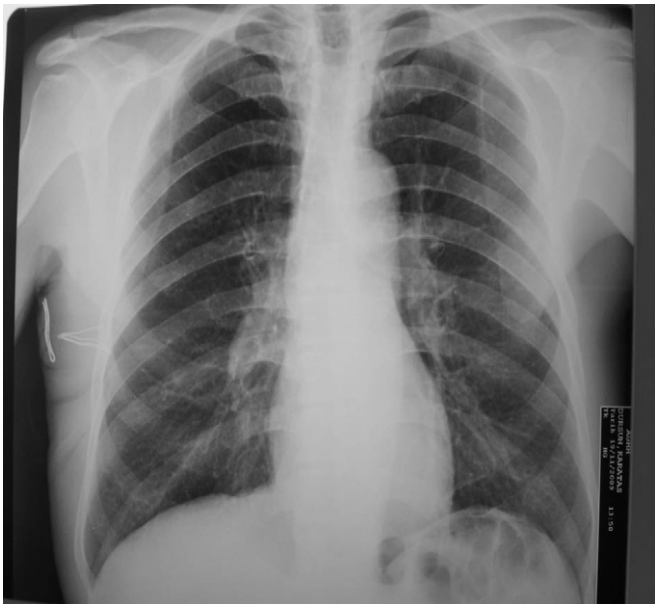

Fig. 1. Tularemia: normal chest X-ray.

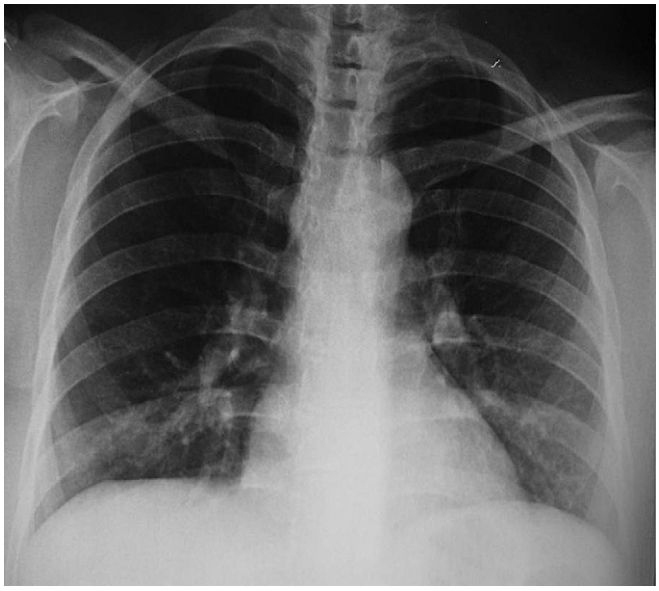

Fig. 3. Idiopathic granulomatous mastitis: normal chest X-ray.

negative for AFB. Chest radiography was normal (Fig. 3). Three sputum smears AFB and TB cultures were negative. Fiberoptic bronchoscopy was normal and bronchial lavage AFB and TB culture was negative. PPD was negative. ESR was 9 mm/h. Serum ACE, calcium and urinary calcium levels were within normal range. Serum tumour marker levels were normal. All other laboratory findings were normal. Abdominal and neck US examinations were normal. Despite of all examinations, there could not be found any finding related with TB, fungal disease, parasitary disease, and other diseases causing granulomatous lesions. This case was suggested idiopathic granulomatous mastitis (IGM).

5. Discussion

Diagnosis of granulomatous inflammation is a common practice in pathology. The common causes of granulomatous reaction are infective agents like mycobacteria, fungi, parasites, etc. and non-infective aetiologies like sarcoidosis, foreign bodies, Wegener's granulomatosis, Crohn's disease, etc. In addition, certain neoplasms are also known to be associated with a granulomatous response in the parenchyma e.g. Hodgkin's disease.[1–3] Differential diagnosis and management demand a skilful interpretation of clinical findings and histology.

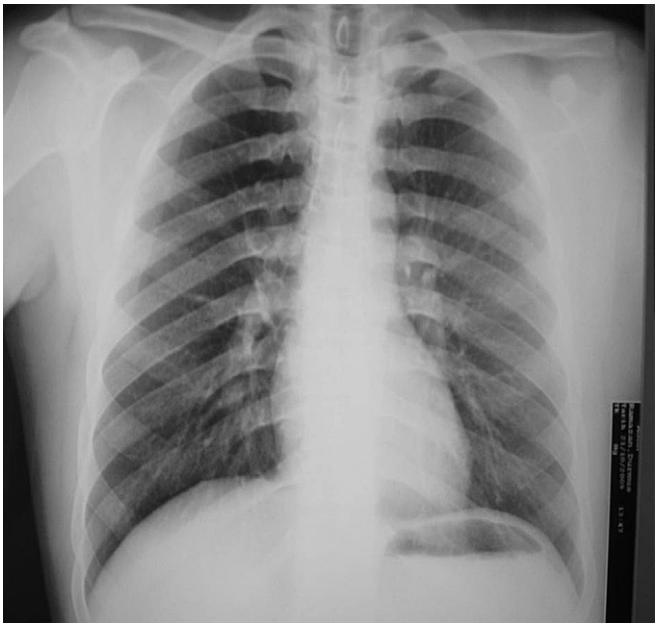

Fig. 2. Cat-scratch disease: normal chest X-ray.

Infections are the commonest causes of disseminated granulomatous disease. Some experts regard an infection as the root cause of all such disorders but that it still remains undetected in some; over the past decade advances in molecular diagnostic techniques have allowed identification of causal organisms that were previously unrecognised.[4]

Tularemia is caused by bacterium *Francisella tularensis*. It occurs naturally in rabbits, hares and rodents. *F. tularensis* can be transmitted to humans via various mechanisms: Bites by infected arthropods, direct contact with infected animals, handling of infectious animal tissues or fluids, direct contact with contaminated soil or water, ingestion of contaminated food, water, or soil, inhalation of infectious aerosols.[5–8]

Because of the difficulty in culturing *F. tularensis*, most cases of tularemia are diagnosed on the basis of clinical picture and/or serology.[9,10] The diagnosis of human cases of tularemia is usually confirmed by the demonstration of an antibody response to *F. tularensis*, which occurs about 2 weeks after the onset of the disease.[11] The detection of serum antibodies is most frequently achieved by agglutination or an ELISA.[11] Commercially available antigens can also be used with standard tube agglutination tests. A fourfold increase during illness or a single titer of 1:160 or greater is considered diagnostic.[12] In first case, axillary LAP biopsy was reported as suppurative granulomatous lymphadenitis. He was referred to our clinic with presumptive diagnosis of TB. All other granulomatous inflammation reasons, primarily TB, had been excluded with clinical, laboratory and radiological findings. Because of history of thorn prick, Francisella tularensis agglutination test was performed.

CSD only occurs in humans, especially those who are scratched or bitten by kittens and then develop regional lymphadenitis proximal to the site of injury. Primary involvement is that of the lymph nodes, which first show lymphoid hyperplasia. Later,

scattered granulomas with central areas of necrosis coalesce to form abscesses. *Bartonella henselae* is the responsible Gram negative bacillus.[13] The clinical diagnosis of CSD is based on the detection of an enlarged lymph node and possibly a skin lesion at the contact site. Clinicians should investigate the patient's contact history with cats, dogs, rodents, fleas, ticks, or other blood sucking arthropods. Pathology suggestive for *B. henselae* infection includes granuloma formation, with microabscesses and follicular hyperplasia.[14,15] The laboratory diagnostic approaches include culture, histological, serological,and molecular methods.[16] The culturing of Bartonella is still a complicated process.[17] A more practical means of laboratory diagnosis is serology for *B. henselae* antibodies, Disadvantages to serologic diagnosis include variable sensitivity and specificity, inability to distinguish between active versus prior infection, and lack of Bartonella species-specific antibody response, resulting in cross-reactivity.[14,15] The majority of CSD cases resolve spontaneously and do not require antibiotic treatment. In complicated CSD, treatment with trimethoprim-sulphamethoxazole, ciprofloxacin or azithromycin is recommended, with gentamicin being reserved for the severely ill patient.[18]

In our case axillary LAP biopsy reported as micro abscess and necrotizing granulomatous lymphadenitis. All other granulomatous inflammation reasons, primarily TB, had been excluded with clinical, laboratory and radiological findings. With detailed anamnesis, it was learned that he had a history of cat bite 1 month ago. We saw skin lesion at the contact site**.** So he was diagnosed as CSD depending on clinical and histological findings. During 3 months follow-up LAP did not recur.

IGM is a rare breast disease of unknown etiology which tends to occur in young females.[19] It is characterized by a tender mass in the breast, mimicking the clinical and radiological features of carcinoma. In addition to TB, leprous, and bacterial infections such as brucella, fungal infections, and parasitic infections, and foreign substance reactions may also lead to granulomatous mastitis.[20–22] IGM may be seen in women aged between 17 and 82, with a mean occurrence age of 30–34.[20–23] Even though some previous studies have claimed that IGM develops within 2 years after childbirth and is associated with nursing, oral contraceptive use, and hyperprolactinemia, these are not valid for all cases.[24,25] For the IGM diagnosis to be made, it is imperative that all other granulomatous mastitis reasons, primarily TB, be excluded after the detection of granulomatous inflammation in the histopathological examination.[22] Complete resection or corticosteroid therapy can be recommended as the optimal treatment. Since 38% of patients experience recurrence, long-term follow-up is indicated.[26] Our case had no history of childbirth, nursing, oral contraceptive use, hyperprolactinemia within 2 years. Breast tissue biopsy revealed noncaseating lobular granulomas with no evidence of malignancy. Serum tumour marker levels were normal. Tissue, sputum and bronchial lavage samples AFB and TB cultures were negative. All other laboratory findings and abdominal and neck US examinations were normal. PPD was negative. Despite of all examinations, there could not be found any finding related with TB, fungal disease, parasitary disease, and other diseases causing granulomatous lesions. This case was suggested IGM. During 9 months follow-up breast tissue US was normal.

In countries with high incidence of TB, TB is considered firstly in differential diagnosis of granulomatous diseases. Detailed anamnesis and physical examinations should be done in differential diagnosis of granulomatous diseases, and TB must be excluded. So unnecessary drug use and treatment costs, drug side affect can be prevented.

Conflict of interest statement

All authors have read and approved the final manuscript and also that the manuscript has not been published and is not being considered for publication elsewhere. We did not take any financial support or supplies in this study. We did not have any commercial or proprietary interest in any drug, device, or equipment. We did not have any financial interest.

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