

Unusual manifestations of brucellosis: a retrospective case series in a tertiary care Greek university hospital

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مظاهر غير معتادة لداء البروسيلات: دراسة استيعادية لسلسلة حالات في مستشفى الجامعة اليونانية للرعاية الثالثة

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الخلاصة: لا يزال داء البروسيلات من المعضلات التشخيصية. وقد أجرى الباحثون دراسة استيعادية للملاحظات المدونة حول الحالات لدى 105 مريضاً مصاباً بداء البروسيلات، ممن أدخلوا في قسم الطب الباطني في جامعة بطرس، وهي مؤسسة للرعاية الثالثة، تقدم خدماتها لمناطق ريفية واسعة في غرب اليونان، وذلك في المدة من 2003 إلى 2006. وتعرف الباحثون على خمسة مظاهر غير معتادة لداء البروسيلات، وهي: المرض الكبدي بالركود الصفراوي داخل الكبدي، والخراجات الكبدية، وخراجات ظاهر الجافية وخراجات الدرقية، وقلة الكريات الشاملة. ومن وجهة نظر افتراضية فإن كل عضو أو جهاز لدى الإنسان يمكن أن يصاب بداء البروسيلات، ويوضح هذا الأمر مدى الحاجة لإدراج داء البروسيلات في التشخيص التفريقي، ولاسيما في المناطق الموطونة به.

ABSTRACT Brucellosis remains a diagnostic puzzle. We retrospectively studied the case notes of 105 patients with brucellosis who were admitted in the Department of Internal Medicine of the University of Patras Hospital, a tertiary care institution serving an extended rural area in western Greece, from 2003 to 2006. Five unusual causes of brucellosis were identified: hepatic, epidural and thyroid abscesses, intrahepatic cholestatic liver disease and pancytopenia. Virtually every human organ and system can be involved in brucellosis, which highlights the need to include brucellosis in the differential diagnosis, especially in endemic areas.

Manifestations inhabituelles de la brucellose : série de cas rétrospective dans un hôpital universitaire de soins tertiaires en Grèce

RÉSUMÉ La brucellose reste une énigme en termes de diagnostic. Nous avons étudié rétrospectivement les notes prises sur les cas de 105 patients atteints de brucellose, admis entre 2003 et 2006 dans le service de médecine interne de l'hôpital universitaire de Patras, établissement de soins tertiaires qui dessert une zone rurale étendue à l'ouest de la Grèce. Cinq causes inhabituelles de brucellose ont été identifiées : abcès hépatique, épidural et thyroïdien, cholestase intra-hépatique et pancytopenie. Quasiment tous les organes et systèmes de l'organisme peuvent être impliqués dans cette maladie, ce qui souligne la nécessité d'inclure la brucellose dans le diagnostic différentiel, en particulier dans les zones d'endémie.

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Received: 20/02/08; accepted: 07/05/08

Introduction

Brucellosis continues to pose a human health risk worldwide, regardless of efforts to eradicate the disease from domestic animals. At present, *Brucella melitensis* represents the principal cause of human brucellosis in most countries, including Greece.

Brucellosis remains a diagnostic puzzle due to its ambiguous, non-specific manifestations and increasingly unusual presentations. The disease is one of the great "imitators" in the universe of infectious diseases, with its ability to mimic various other diseases. The most common sites involved are osteoarticular, especially sacroiliitis (20%–30%) with large joints most frequently affected in children, and the genitourinary system, especially epididymo-orchitis (2%–40% of males). Unusual manifestations of brucellosis, with a prevalence rate lower than 5% of cases, are neurobrucellosis (1%–2%) which usually presents as meningitis, endocarditis (1%) (mostly left-sided) and hepatic abscess (1%). There are other exceptionally rare manifestations including thyroid, splenic and epidural abscess, pneumonitis, pleurisy or empyema and uveitis.

This retrospective case series assembles our recent experience of the diagnostic challenges in combating this protean disease in an endemic area of western Greece. From the 105 case-notes we studied, the 5 cases of brucellosis reported in this paper all had an atypical and misleading presentation and all constituted a life-threatening clinical situation. They highlight the need for vigilance by physicians and close collaboration with the microbiology department to swiftly diagnose and treat this infection, in order to avoid deleterious consequences. Laboratory testing is indispensable for diagnosis and should always be combined with a high index of clinical suspicion. Establishing a history of travel to endemic countries plus exposure to animals and/

or their products is crucial in order to reach an early clinical diagnosis.

Case reports

Case 1

A 67-year-old previously healthy farmer presented to our hospital in March 2003 with fever up to 40 °C, rigor, fatigue and abdominal pain of 5 days' duration. He mentioned frequent consumption of unpasteurized dairy products. On examination he looked moderately ill, and right quadrant tenderness along with a positive Murphy sign was noted.

Laboratory tests showed the following values: haematocrit (Ht) 36%, white blood cell count (WBC) 4000 cells/mm³ (neutrophils 60%, lymphocytes 24%, monocytes 12%, basophils 3%, eosinophils 1%) and platelet count (PTL) 133 000/mm³ (normal range: 150 000 to 450 000/mm³). Erythrocyte sedimentation rate (ESR) was 107 mm in 1 hour. Liver function tests were abnormal: aspartate aminotransferase (AST) 155 U/L (normal range: 5–40 U/L), alanine aminotransferase (ALT) 281 U/L (normal range: 5–40 U/L), gamma-glutamyl-transpeptidase (γ GT) 143 U/L (normal range: 10–75 U/L), alkaline phosphatase (ALP) 185 U/L (normal range: 35–125 U/L) and lactate dehydrogenase (LDH) 680 U/L (normal range: 80–230 U/L). All other laboratory findings were within normal limits.

Abdominal ultrasonography revealed mild hepatomegaly. *Brucella* agglutination test was negative. The patient was empirically treated with ciprofloxacin 400 mg every 12 hours and metronidazole 500 mg every 8 hours. On day 4 his clinical condition worsened and a new ultrasound revealed an enlarged gall bladder with thickened wall, suggesting an empyema. Abdominal computerized tomography (CT) scanning demonstrated mild hepatosplenomegaly and a hepatic lesion with

central necrosis, consistent with the abscess. The patient was transferred to the surgical ward and operated on the same day. A cholecystectomy and aspiration of the abscess were performed.

Two days later, *B. melitensis* was isolated from 2 blood cultures that had been drawn on admission. *B. melitensis* was also cultured from the aspirate of the liver abscess. Gallbladder biopsy revealed acute cholecystitis, but gallbladder culture was negative. Antibiotic treatment was changed to doxycycline 200 mg/day, rifampicin 900 mg/day and gentamycin 240 mg/day. The patient was discharged on day 14 and was prescribed doxycycline 200 mg/day with rifampicin 900 mg/day for 3 months.

Case 2

A 41-year-old man with no past medical history presented in June 2003 and was admitted to our hospital complaining of acute low back pain of 10 days' duration. The pain progressively worsened and 2 days before admission he started to suffer fever with rigors, malaise and profuse night sweating. On physical examination, only low back tenderness was noted.

Laboratory tests showed the following values: Ht 43%, WBC 19 000 cells/mm³ (neutrophils 83%, lymphocytes 15%, monocytes 2%), PLT 450 000/mm³, ESR 120 mm/h, C-reactive protein (CRP) level 11 mg/dL (normal range: 0.08–0.8 mg/dL). All other laboratory findings were normal. The Wright agglutination test for *Brucella* was positive at titres of 1:320.

A magnetic resonance imaging (MRI) study was performed. On the pre-contrast T1-sagittal images, a collection of fluid with low signal intensity was detected in the posterior epidural space that was anteriorly compressing the dorsal sac. A decreased signal intensity of the L5 and S1 vertebral bodies was also demonstrated. Following gadolinium (Gd) administration, there

was marked enhancement of the L5 and S1 vertebral bodies, the L5-S1 intervertebral disk and the epidural fluid collection, consistent with spondylo-discitis and abscess formation at the L5-S1 level. While awaiting blood culture results, meropenem and vancomycin intravenously were administered along with rifampicin and doxycycline *per os*. The fever subsided the next day but the low back pain remained unchanged and was intensified when the patient's right leg was elevated at 35°.

On the 6th hospital day, blood cultures revealed *B. melitensis*. The patient was operated on the same day and a broad L5 laminectomy was performed with complete abscess removal and decompression of the S1 nerve root. *B. melitensis* was also isolated from the abscess. The patient's postoperative course was uneventful and he was discharged 7 days after surgery. Rifampicin 600 mg/day and doxycycline 200 mg/day were administered for 3 months.

Case 3

An 87-year-old woman suffering from mild hypertension and rheumatoid arthritis first presented in April 2004 and was urgently admitted to our hospital because of fever up to 38 °C, severe neck pain and difficulty swallowing solids and liquids of 12 days' duration. She was on oral methylprednisolone (8 mg/day).

On physical examination the enlarged thyroid gland was very tender to palpation. There was a large swelling occupying the region of the thyroid gland, the overlying skin was warm and erythematous, but no fluctuation was apparent. Swallowing aggravated the pain. Blood and urine cultures were obtained and ticarcillin-clavulanate in combination with vancomycin was administered intravenously.

Laboratory evaluation demonstrated a leukocyte count of 5300 cells/mm³ (60% neutrophils, 27.7% lymphocytes, 8.5% mononuclear cells, 3.4% eosinophils and 0.4% basophils). Ht was

36%, haemoglobin (Hb) 11.1 g/dL and PTL count 190 000 /mm³; ESR was 106 mm/h and blood biochemistry profile was normal. The Wright agglutination test for *Brucella* was positive at titres of 1:640. A computerized tomography of the thyroid revealed 2 cystic areas in the right lobe and the isthmus of the gland which did not enhance with contrast.

A fine-needle aspiration of the thyroid fluctuant mass was performed, and culture yielded *B. melitensis*. Blood cultures also isolated *B. melitensis*. Rifampicin 600 mg/day and doxycycline 200 mg/day were added to the antibiotic regimen. A detailed history revealed that the patient was occasionally consuming unpasteurized milk and fresh cheese. The patient's condition deteriorated over the next 2 days, with high fever and development of necrotic skin areas and sinus tracts over the fluctuant right lobe mass. She was operated on and the right thyroid lobe and isthmus were removed.

The patient had an uneventful course and was discharged 5 days after the operation. A barium esophagogram performed after her discharge failed to show a pyriform sinus fistula (PSF). Rifampicin 600 mg/day and doxycycline 200 mg/day were prescribed for 3 months, and doxycycline alone was administered for 6 more months.

Case 4

A 39-year-old shepherd presented to the emergency department in February 2005 and was admitted with fever up to 40 °C, rigors, fatigue and abdominal pain of 7 days' duration. On examination, he looked unwell, and a diffuse abdominal tenderness was noted. Neither lymphadenopathy nor hepatosplenomegaly was noted.

Blood analysis on admission showed pancytopenia (Hb 9.1 g/dL, Ht 29.2%, total WBC 1150/mm³ with a neutrophil count of 450/mm³, PTL 98 000/mm³ and reticulocytes 0.2%. Blood smear examination revealed non-

specific findings. CRP level was elevated (19.5 mg/dL). Liver function tests were mildly elevated (AST 48 U/L, ALT 52 U/L, γ GT 75 U/L and LDH 343 U/L). All other laboratory findings were within normal limits.

Brucella agglutination test was negative. On day 4, bone marrow aspiration cultures and biopsy was performed. Bone marrow aspirate revealed hypocellularity, which was confirmed by bone marrow biopsy. Granulomas were not present in the bone marrow biopsy. He had a normal chest radiograph. Abdominal ultrasonography and CT scanning were normal.

The patient was empirically treated with meropenem 1g \times 3 and vancomycin 1g \times 2. *B. melitensis* was isolated from 2 blood cultures and bone marrow cultures. Antibiotic treatment was switched to doxycycline 200 mg/day, rifampicin 900 mg/day and gentamycin 240 mg/day. Pancytopenia was resolved during treatment and the patient was discharged on day 14, with doxycycline 200 mg/day and rifampicin 900 mg/day for 2 months.

Case 5

A 50-year-old woman presented in October 2006 and admitted to our hospital on the same day because of low-grade fever of 10 days' duration, malaise, anorexia and sweating. She had an unremarkable medical history. Consumption of unpasteurized dairy products during the previous month was recorded.

Physical examination revealed mild hepatomegaly and splenomegaly, confirmed by an abdominal ultrasound and CT imaging. Laboratory evaluation showed: Ht 34%, WBC 5700 cells/mm³ (neutrophils 62%, lymphocytes 28%, monocytes 8%, eosinophils 2%), PLT 119 000 /mm³, ESR 85 mm/h, CRP 8.95 mg/dL, ALT 527 U/L, AST 692 U/L, GGT 455 U/L, ALP 437 U/L, bilirubin 4.7 mg/dL, direct bilirubin 2.4 mg/dL, albumin 3.5 g/dL and LDH

492 U/L. *Brucella* agglutinin titre was positive at 1/640. Blood cultures isolated *B. melitensis* on day 7.

Doxycycline was administered (100 mg *per os* twice daily) for 6 weeks plus 1 g streptomycin intramuscularly for the first 21 days, beginning on the 3rd day of hospitalization, while waiting for the serological and cultural confirmation. Liver dysfunction gradually improved and was finally completely restored 1 month after discharge.

Discussion

Case 1

Hepatic involvement in infections caused by *Brucella* spp. is common (in 50% of patients), but the production of single or multiple liver abscesses is exceptional, with an incidence of only 0.2% [1]. A review of the medical literature showed only 40 cases from 1904 until now, almost all involving adults with chronic infection [2,3]. In most reported cases of brucellar abscess, fever is the main symptom. Two-thirds of patients had prolonged, slight pain in the right upper abdominal quadrant.

The most significant laboratory disturbances include increased ESR and normochromic, normocytic anaemia in half the patients, with no leukocytosis or leukopenia, and a normal or slightly neutrophilic differential count [4]. Liver function tests commonly portray an increase in cholestasis-dependent enzymes with values 4- to 5-fold above normal values in 50% of cases, generally with no increased bilirubin or transaminases.

Ultrasound most commonly shows a single, hypoechoic, lesion with ≥ 1 centrally located calcium deposits [5]. CT findings most frequently portray a hypodense area, and often ≥ 1 saccular, loculated forms, and ≥ 1 calcifications [5]. The presence of central calcifications is a very common finding, particularly in long-standing involvement, which

should alert the physician to the possibility of a brucellar abscess [4].

In our case, suppurative disease of the liver developed in the acute phase of the disease. This may be observed in prolonged, recurrent brucellosis, but is quite rare in acute brucellosis. The absence of calcium deposition in the liver abscess, a constant characteristic of hepatic suppurative complications in chronic brucellosis, was also confirmation of the acute form of the disease in our patient.

Case 2

Spinal epidural abscess (SEA) is a rare condition, which is difficult to diagnose, may be complicated by potentially disastrous neurological or vascular complications and can be fatal if left untreated. SEA accounts for 1–2 in every 10 000 hospital admissions, and *Staphylococcus aureus* is the agent most frequently implicated [6]. *Brucella* spp. are responsible for only 0.1% of cases. Risk factors include immunocompromised states, but no predisposing conditions are found in 20% of patients. Skin abscesses and furuncles represent the most common source of infection. The most common presenting symptoms of SEA are back pain and fever, and the lapse between the onset of pain and neurologic deficits is quite varied. Neurologic dysfunction is often disproportionate to the observed degree of compression and a combination of compressive and ischaemic effects may act in synergy to produce the deleterious sequelae of epidural abscess. MRI has the greatest diagnostic accuracy and is the method of first choice in the diagnostic process [7]. Typical MRI findings in vertebral osteomyelitis include decreased signal intensity in the disk and adjacent vertebral bodies on T2-weighted images, loss of endplate definition on T1-weighted images and contrast enhancement of the disk, adjacent vertebral bodies and involved paraspinal and paravertebral soft tissues on T1-weighted images [8].

The therapeutic method of choice is laminectomy and drainage of the abscess combined with antibiotics.

Case 3

Infections of the thyroid are rare because the gland is resistant to infection. Hendrick reported that only 5% of 117 reviewed patients with thyroiditis finally developed an abscess [9]. Infectious thyroiditis may be either acute or chronic. Acute suppurative thyroiditis (AST) can lead to abscess formation if left untreated, and is usually caused by Gram-positive or Gram-negative organisms; *S. aureus* predominates, but pneumococcal, *Salmonella* spp., mycobacterial, parasitic, fungal and pneumocystic infections may also occur. AST most likely occurs in patients with pre-existing thyroid disease, with congenital anomalies such as a PSF, with immunosuppression, with the acquired immunodeficiency syndrome (AIDS) and in elderly or debilitated patients. AST usually presents with pain, tenderness and fever. Sore throat, dysphonia and dysphagia may also be present. Haematogenous seeding from a distal site of infection may be the most common cause of thyroid infection, although the precise infectious source is often unidentified [10].

Laboratory features include elevated ESR and possibly an elevated WBC with a left shift. Radioactive iodine scanning may be normal or show suppurative areas appearing as "cold" nodules. Ultrasound and CT scanning may demonstrate the abscess. Most authorities agree that a barium oesophagogram should be done after the infective process subsides to look for an occult PSF [11]. In these cases, reconstructive surgery is essential to prevent recurrence of the abscess. The essential steps in evaluation are fine-needle aspiration biopsy, with Gram staining and culture of the thyroid to identify the causative organism. Surgery is the most frequently recommended

management of a thyroid abscess, either excision or drainage, combined with suitable parenteral antibiotic treatment, although it has been suggested that thyroid abscesses can be treated with antibiotics alone and surgery should be employed only if antibiotics are unsuccessful [12].

Case 4

Brucellosis is related to an assortment of nonspecific haematological abnormalities. Akdeniz et al. documented anaemia in 55% of their patients, leukopenia in 21%, thrombocytopenia in 26%, and pancytopenia in 8% [13]. The pathogenesis of pancytopenia is poorly understood, but hypersplenism [14], haemophagocytosis [15], and granulomatous lesions of the bone marrow [16] seem to be implicated. Haemophagocytosis has been documented in 10%–30% of patients with brucellosis, and in 87% of patients with pancytopenia caused by this disease [16]. Pancytopenia is not a rare manifestation, with an incidence varying from 2% to 21% and bone marrow aspiration specimens usually reveal normo- or hypercellularity [17].

In this case, the patient presented only with febrile pancytopenia, demonstrating bone marrow hypoplasia, which is a rare feature of brucellosis. There was no haemophagocytosis or granulomatous infiltration of the bone marrow. Hepatosplenomegaly and bone marrow hyperplasia, indicating that pancytopenia may be due to

hypersplenism [18], were also absent in our patient. Physicians should always keep in mind the possibility of brucellosis in febrile neutropenic patients or those presenting with aplastic anaemia, especially if the patients are living in, or have travelled to, endemic areas.

Case 5

Brucellosis involves the liver in different modes. Hepatitis is frequent, usually manifested as a mild increase of transaminases, while liver abscess or jaundice are uncommon [19]. Ascites may be present, either as a temporary exacerbation of pre-existing hepatic disease or as frank peritonitis [20]. Asymptomatic, mild cholestatic hepatitis accounted for approximately 16% of acute cases of brucellosis in a small study from Greece [21]. Granulomas can be present in liver-biopsy specimens in cases of both *B. melitensis* and *B. abortus*. Akritidis et al. demonstrated granuloma development in the liver parenchyma in all patients and in the portal spaces in a majority of patients [22]. Varying degrees of cellular infiltration of parenchymal tissue and portal spaces, giant cells in granulomas, parenchymal necroses and Kupffer cell hyperplasia were also noted.

Conclusions

Virtually every human organ and system can be involved in brucellosis, a fact that emphasizes the importance of always

including brucellosis in the differential diagnosis, especially in endemic areas, even if the clinical aspects are not entirely consistent with it.

Although liver abscess formation is rarely observed in the chronic stages of brucellosis, acute cholecystitis and suppurative liver disease may be the main manifestations during the acute phase.

Brucella infection should be considered in patients presenting with signs and symptoms of spinal epidural abscess, a rare but devastating condition if not diagnosed early and treated promptly and effectively.

Infections of the thyroid are quite rare, but progress to abscess formation may occur, with all the deleterious consequences of advanced suppuration in the neck. *Brucella* spp. are very rarely implicated in the pathogenesis of this disease, but should be considered as the etiologic agent especially in elderly, debilitated patients.

Brucellosis may present as febrile neutropenia or even as aplastic anaemia, and bone marrow cultures are the gold standard in isolating the organism.

Finally, although liver involvement in brucellosis is usually manifested by a mild increase in transaminases, a frank cholestatic hepatitis may also occur and the patient may be subjected in unnecessary, time-consuming, costly and invasive interventions if *Brucella* is not included in the differential diagnosis.

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