

Unusual Sites of Tuberculosis in Patients with Rheumatologic Conditions

Hernandez, A.T.S.*; Magbitang, A.T.D.*; Gutierrez- Rubio, A.K.*; Manapat- Reyes, B.H.**

Abstract

Introduction: Tuberculosis (TB) is a chronic infectious disease, with a growing incidence seen worldwide. Among the tuberculous infections, pulmonary TB remains to be the most common, with extra-pulmonary TB seen in only less than 2.0% of this population. Although the latter remains to be rare, it is commonly found in the lymph nodes, gastrointestinal (GI) and genitourinary (GU) tracts, weight-bearing joints, and the meninges. But, however rare extra-pulmonary tuberculosis may be, some patients have reported the occurrence of such in less common sites.

In patients with autoimmune diseases, the diagnosis and management of microbial infections remain complicated because of their immunocompromised nature, and because of the medications they receive. As tuberculosis is a curable disease, early identification and proper treatment should be applied to avoid further patient compromise.

Objective: The objective of this paper is to present three cases of patients diagnosed with extra-pulmonary tuberculosis at atypical sites namely tuberculous cellulitis, endometrial tuberculosis, and tuberculous dactylitis, accompanying a primary

rheumatologic disease.

Cases: Case 1 is a patient with Dermatomyositis who presented with pain and non-traumatic ecchymosis on his right gluteus, later diagnosed as TB cellulitis through a positive AFB smear of the aspirate. Case 2 is a patient with SLE whose amenorrhea was initially attributed to Cyclophosphamide. However, further work up revealed tuberculous bacteria through AFB smear of the curetting, hence was diagnosed with Endometrial TB. Case 3 reports another patient with SLE, who was diagnosed with recurrent TB dactylitis through a positive AFB smear of the biopsy.

Conclusion: Despite the high endemicity of the Philippines for tuberculosis, extra-pulmonary TB continues to be underrecognized. Patients with autoimmune conditions are most likely to suffer from such infections due to their immunocompromised state. High suspicion and management remain to be the cornerstone to avoid diagnostic delays, and improve outcome.

Keywords: autoimmune, tuberculosis, dermatomyositis, systemic lupus erythematosus, extra-pulmonary

Background

Tuberculosis (TB) is a chronic infectious disease seen worldwide. Its incidence is increasing every year particularly in developing countries.¹ In the Philippines, patients diagnosed with the disease have been reported to be increasing and it remains to be one of the most common causes of morbidity and mortality. Pulmonary TB has remained to be the most prevalent, accounting to 98.6% of diagnosed TB cases.² Extra-pulmonary manifestations of the disease

occur in a smaller percentage, which may lead to a delay in diagnosis and treatment. Common sites of EPTB include the lymph nodes, pleura, meninges, GI tract, kidneys, and the weight-bearing joints. Tuberculosis is known to affect patients in all disease spectra, particularly those with impaired immunity. Patients with rheumatologic conditions, especially autoimmune diseases, are considered to be susceptible to mycobacterial infection, because of the immunocompromised state and the medications used in their treatment. Compared to the general population, the prevalence of extrapulmonary tuberculosis is higher^{3,4,5,6}. However rare cases of extra-pulmonary tuberculosis may be, there appears to be a smaller number of cases that fall to atypical EPTB. Due to the immunocompromised nature of patients with rheumatologic conditions and due to the probable event of masking classic symptoms, the objective of our paper is to report three cases of patients with rheumatologic diseases diagnosed with

*Fellow in training, Section of Rheumatology, Department of Medicine, Philippine General Hospital, Manila, Philippines

**Faculty, Section of Rheumatology, Department of Medicine, Philippine General Hospital, Manila, Philippines

Corresponding Author: Ana Hernandez, MD, Philippine General Hospital, Taft Avenue, Manila, Philippines
Email: ana.hernandezmd@yahoo.com

tuberculosis at unusual sites.

Case 1

A 32-year-old married Filipino male, came at our clinic with photosensitive rashes on the face and neck, associated with proximal muscle weakness and arthralgias. Work-up revealed ANA +4 speckled, EMG- NCV showing active myopathy, and elevated CK- Total and CKMM. Due to these findings, he was diagnosed with Dermatomyositis and was initially managed with high-dose prednisone at 1/.0mg/kg/day, with improvement of symptoms.

Five months from the diagnosis of his condition, the patient complained of pain and swelling of the right gluteal area, with pain radiating to the right thigh. He self-medicated with herbal medicines, but noticed that the affected area became more painful and erythematous. He was treated for cellulitis with clindamycin 300mg 1.0 tab every six hours, which did not improve his condition, hence was admitted. x-ray of the right hip did not show osteomyelitis. Ultrasound of the affected area revealed markedly thickened and edematous subcutaneous and muscular layers. He was started on Ceftriaxone 2.0g IV OD, and Clindamycin was continued. However, despite five days of IV antibiotics, no improvement was noted, and patient was reported to have intermittent febrile episodes. Aspiration of the area was done and specimen was sent for analysis. AFB Smear was noted to be +2, thus a diagnosis of tuberculous cellulitis was made. Antibiotics were then discontinued and patient was treated with isoniazid, rifampicin, pyrazinamide and ethambutol, with improvement of symptoms. Throughout the course, prednisone was maintained at low-dose, and dermatomyositis remained controlled.

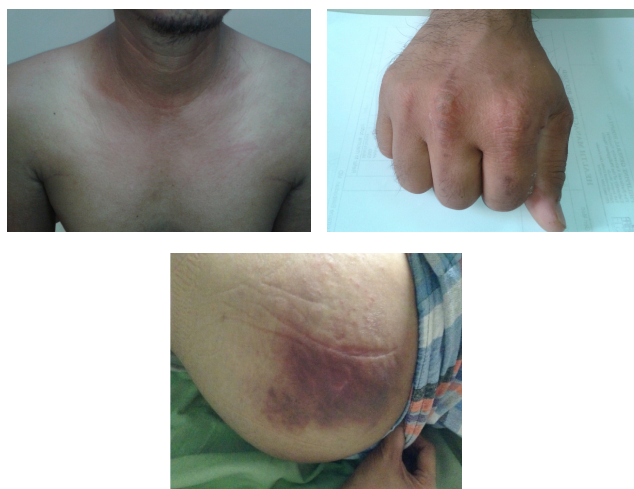


Figure 1: a) v- shaped rash, b) gottron's rashes, c) gross picture of affected area initially managed as cellulitis, with aspirate later proven positive for AFB.

Case 2

A 32-year-old single Filipino female was initially diagnosed with systemic lupus erythematosus when she was 25 years of age after presenting with arthritis, photosensitivity, malar rash, discoid rashes, oral ulcers, leukopenia with lymphopenia, high titers of antinuclear antibody (ANA) with a homogenous pattern on immunofluorescence, and 4.6 grams of urinary protein in 24 hours. Renal biopsy was done which showed lupus nephritis (LN) modified WHO Class IIb. She was treated with prednisone at 1.0 mg/kg/day, hydroxychloroquine 200 mg/day, and the NIH protocol of cyclophosphamide intravenous infusion. No untoward events were noted at that time. Her lupus activity went into remission after cyclophosphamide induction and prednisone was tapered to a maintenance dose of 2.5 mg per day.

On the seventh year of her illness, the patient experienced lupus nephritis flare with significant proteinuria of 1.14 grams per day, pyuria and hematuria on urinalysis. She was treated with high dose prednisone (1.0 mg/kg/day) and cyclophosphamide IV infusion using the EUROLUPUS protocol (cyclophosphamide 500 mg intravenously every two weeks for six sessions). She improved with resolution of significant proteinuria and prednisone was decreased to 0.3 mg/kg/day. However, after completion of cyclophosphamide therapy, she reported a two-month history of amenorrhea and a one month history of vaginal spotting, with no other associated symptoms. Because of her recent treatment with cyclophosphamide, an impression of possible premature ovarian failure secondary to cyclophosphamide therapy was entertained.

Initial gynecologic evaluation was unremarkable, however, transvaginal ultrasound showed a thickened endometrium. Dilatation and curettage with endometrial biopsy were performed. Histopathology of endometrial curettings revealed chronic granulomatous endometritis with Langhans type giant cells consistent with a tuberculous etiology (Figure 2). Endometrial tuberculosis was diagnosed.

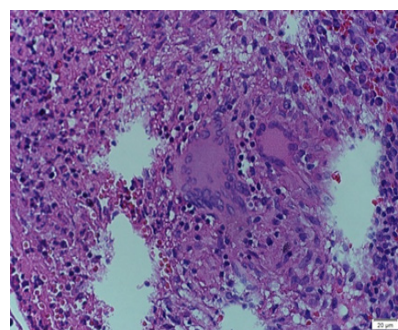


Figure 2: Histopathology of endometrial curetting showing Langhans giant cells.

Acid-fast bacilli (AFB) smears of the sputum, stool and urine were all negative. We treated the patient with anti-tuberculous (TB) therapy for nine months. The patient showed favorable response to treatment with resumption of her normal menstrual flow and resolution of abnormal uterine bleeding occurring after the first month. This was sustained throughout the course of anti-TB therapy. We performed a post-treatment transvaginal ultrasound and endometrial biopsy which showed a normal endometrium and absence of chronic granulomatous endometritis and Langhans cells. Her SLE disease activity remained controlled.

Case 3

A 34-year-old married Filipino female with systemic lupus erythematosus (SLE) came to our clinic complaining of a painful nodular mass on the left palm, overlying the second metacarpal. She was diagnosed with SLE at the age of 22, based on the initial presentation of prolonged fever, polyarthritis, leukopenia and lymphopenia, proteinuria (daily urine protein of 450mg) and high titers of antinuclear antibodies (ANA) with a homogenous pattern on immunofluorescence. Pathology of renal biopsy revealed lupus nephritis WHO Class II. She was treated with oral prednisone (initial dose 0.7 mg/kg/day). Disease activity improved, and patient spent several years in remission with a minimum steroid dose of 5mg/day. On the tenth year of illness she had sudden right sided weakness due to a left middle cerebral artery infarct. She was treated with antiplatelets, statins, and antihypertensive medications and improved significantly with physical therapy. Antiphospholipid antibody and lupus anticoagulant tests were negative. She continued to require only minimal doses of oral prednisone to control disease activity.

On the 11th year of illness, she had low grade fever and swelling of the left index finger. A fluctuant mass developed on the involved area, and was initially managed as cellulitis. However, antibiotics did not resolve symptoms. Analysis of the discharge fluid reported positive for acid fast bacilli, and diagnosis was changed to TB dactylitis. She was treated with anti-tuberculosis therapy for six months with significant decreased pain, swelling and erythema and resolution of the abscess but persistent flexion deformity of the third right distal interphalangeal joint.

On her 12th year of illness, routine urinalysis revealed increasing proteinuria. Daily urine protein was as high as 1.0g, and prednisone was increased to 1.0mg/kg/day. She was also started on hydroxychloroquine. She was advised induction treatment with cyclophosphamide or mycophenolate mofetil. Proteinuria, however, decreased significantly on steroids alone to 350mg/day. Steroid

dose was slowly tapered to 10mg/day. She later complained of severe pain on the palmar side of the left hand over the second flexor tendon. An impression of a Trigger Finger was made. Intralesional steroid injection was done, with initial improvement. Over the next two months, she noted development of a nontender cystic mass over the left second metacarpal and a ganglion cyst was initially suspected. A biopsy of the mass was done, and the fluid was positive for acid fast bacilli. A diagnosis of a recurrent tuberculous dactylitis was then made. Radiographs revealed soft tissue swelling without involvement of the bone or joint. She is currently ongoing anti-tuberculosis treatment with isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin.

Discussion

The association between rheumatologic diseases and tuberculosis has been proposed in several studies worldwide. Among patients with SLE, a six to 60-fold increased risk is reported.^{7,8,9,10,11} In a cohort of 90 patients with other rheumatologic conditions such as rheumatoid arthritis and ankylosing spondylitis for anti-TNF treatment, latent tuberculosis was detected in 37% to 62% using different methods.¹² In a study done by Chen²³ among 192 patients with PM and DM, it was noted that tuberculosis accounted for 9% of infections in these patients. This association may be explained by multiple immune abnormalities in patients with autoimmune conditions and its associated immunosuppressive treatment.^{13,14}

TB infection may be asymptomatic or may present with mild symptoms which lead to difficulty in detection. Even in countries that are endemic to tuberculosis such as the Philippines, those with extra-pulmonary tuberculosis still remain under recognized. This is especially true among patients with rheumatologic conditions where symptoms of TB may mimic manifestations of rheumatologic disease or tuberculous infection may present atypically.⁴ In addition, although it has been previously said that pulmonary TB is a risk factor for the development of extra-pulmonary disease, several reports have stated otherwise.^{15,16}

Case 1, a diagnosed case of dermatomyositis with cellulitis was initially treated with empiric antibiotics but with persistence of condition. Aspiration studies revealed a negative bacterial culture but with an AFB +2. This same scenario was observed in a study reported by Rajalingham et al.¹⁵ wherein a female patient who came in for fever and myalgia was initially treated with empiric antibiotics and antifungals showed progression of symptoms. In this case, a thorough work-up revealed tuberculosis and patient improved with anti-Koch's medications.

Another patient who presented as such was documented by Yoshida et al in 2004^{17,18}. Marie et al. reported *Mycobacterium* species to be among the opportunistic infections in patients with dermatomyositis and polymyositis in a retrospective review among such patients¹⁹. However, present data only report on pulmonary tuberculosis, as only 0.04% of those with extra-pulmonary TB are reported as non-arthritis nor osteomyelitis-related²⁰. Although there have been reported cases of patients with dermatomyositis who developed disease relapse upon initiation of rifampicin, this did not occur in our patient.²¹

In SLE, the presentation of TB differs from that seen in the non-SLE population. TB in SLE features a more extensive pulmonary involvement, a high rate of relapse, disseminated disease and extrapulmonary involvement.^{4,5} In a Turkish study of 556 patients with SLE, the prevalence of TB was 3.6%, 45% of which were extrapulmonary. Across Asia, the percentage of extrapulmonary TB infections in patients with SLE ranges from 18.8% in Singapore to as high as 66.7% in Hong Kong. The extrapulmonary sites most commonly involved are the pleura, meninges, skin joints and kidneys.^{4,5,6,22} In the Philippines, a study done by Navarra et al. in 1996, it was documented that the musculoskeletal, CNS, and gastrointestinal systems were among the more common extra-pulmonary sites affected by the *Mycobacterium*.²³

In the second case, TB infection was detected in the endometrium—an unusual atypical site of TB infection both in SLE and the general population. The incidence of genital TB is less than 1.0% in developed countries.²⁴ In a small retrospective study done locally, genitourinary TB was seen in two out of 54 Filipino patients with both SLE and documented TB.²⁰ At present, there has been no reported case of endometrial TB in SLE. This may be explained by the lack of specific symptoms and the difficulty in detection. The diagnosis is made by *Mycobacterium* culture, histopathology or polymerase chain reaction, however, these tests have sensitivities of only seven to 57%.²⁵ Clinical correlation is still warranted. In the second case presented, the diagnosis was made by the presence of granuloma and Langhans cells in the presence of nonspecific gynecologic symptoms. Clinical response and resolution of abnormal histopathology after anti TB treatment affirmed the diagnosis of endometrial TB.

The third case is one of tuberculous dactylitis in a patient with SLE, first involving the right middle finger, and a year later involving the left second metacarpal. Tuberculous dactylitis in itself is rare in the general population. It is more common among children less than six years old, with an incidence of 0.65-8% in children with TB.^{26,27} In adults the incidence is even lower, with no reported statistics and only

isolated case reports.²⁸ One roentgenical surveys described only three cases of small tubular bone TB in adults among 156 with skeletal involvement, and only two cases of small bone involvement among 100 adults with skeletal TB.^{29,30} Feldman et al. described only 23 cases among 200 skeletal TB patients seen from 1930-1970.³¹ On literature review, there were no reported cases of tuberculous dactylitis among patients with SLE. This may be due to difficulty in diagnosis—patients with tuberculous dactylitis often present with painless swelling over weeks or months, without fever or other systemic symptoms.²⁹ In patients with rheumatologic conditions, these could be misdiagnosed as part of disease activity. Diagnosis is made based on characteristic radiographic features of cystic or diaphyseal expansion of short tubular bones; periosteal reaction and sequestra are uncommon.^{25,29} Definite diagnosis of tuberculous dactylitis is made with bacteriological and histologic studies.²⁴ A high index of suspicion is needed in order to diagnose this disease. In this patient, tuberculous dactylitis was not initially suspected—however, due to the high incidence of TB in this population, acid fast staining was done. Although rare, tuberculous dactylitis must be kept in mind, especially in areas with high incidence of TB and in vulnerable populations, such as patients on immunosuppressants or with connective tissue diseases.

Table 1: Summary of disease features

Diagnosis	TB Cellulitis	Endometrial TB	TB Dactylitis
Age	32 y.o.	32 y.o.	34 y.o.
Gender	M	F	F
Primary Disease	Dermatomyositis	SLE with nephritis	SLE with nephritis
Treatment for Primary Disease	Prednisone	Prednisone HCQ Cyclophosphamide (NIH protocol)	Prednisone HCQ
Prednisone dose at time of TB dx	Low dose	High dose	Low dose

Conclusion

We presented three cases of TB affecting unusual sites among patients with different rheumatologic conditions. In the first and last case, the lack of response to antibiotics prompted the consideration of other organisms. The gold standard of diagnosing EPTB remains to be TB culture, and although no uniform test among these three cases was used, AFB smears or compatible biopsy findings are acceptable. As immunocompromised patients may present atypically, a thorough work-up is warranted. In patients with rheumatologic conditions, evaluation for infection, particularly TB, is important, as this

may impact greatly the disease course, treatment and quality of life.

References

1. **World Health Organization. Global Tuberculosis Report.** World Health Organization Report. 2011.
2. **Vianzon R, Garfin AM, Lagos A, Belen R.** The tuberculosis profile of the Philippines, 2003- 2011: advancing DOTS and beyond. *Western Pacific Surveillance and Response Journal*, 2013, 4(2). doi:10.5365/wpsar.2012.3.4.022.
3. **Franco-Paredes C, Dizon-Borjon A, Senger MA, Barragan L and Leonard M.** The ever-expanding association between rheumatologic diseases and tuberculosis. *Am J Med.* 2006; 119(6):470-7.
4. **Prabu V, Agrawal S.** Systemic lupus erythematosus and tuberculosis: a review of complex interactions of complicated diseases. *J Postgrad Med.* 2010 Jul-Sep;56(3):244-50.
5. **Hodkinson B, Musenge E and Tikly M.** Osteoarticular tuberculosis in patients with systemic lupus erythematosus. *Q J Med* 2009; 102:321-3
6. **Sayarlioglu M, Inanc M, Kamali S, Cefle A, Karaman O, Gul A, Ocal L, Aral O, Konice M.** Tuberculosis in Turkish patients with systemic lupus erythematosus: increased frequency of extrapulmonary localization. *Lupus.* 2004;13(4):274-8.
7. **Erdozain JG, Ruiz-Iratorza G, Egurbide MV, Martinez-Berriotxo A, Aguirre C.** High risk of tuberculosis in systemic lupus erythematosus? *Lupus* 2006;15:232-5.
8. **Mok MY, Lo Y, Chan TM, Wong WS, Lau CS.** Tuberculosis in systemic lupus erythematosus in an endemic area and the role of isoniazid prophylaxis during corticosteroid therapy. *J Rheumatol* 2005;32:609-15.
9. **Tam LS, Li EK, Wong SM, Szeto CC.** Risk factors and clinical features for tuberculosis among patients with systemic lupus erythematosus in Hong Kong. *Scand J Rheumatol* 2002;31:296-300.
10. **Gaitonde S, Pathan E, Sule A, Mittal G, Joshi VR.** Efficacy of isoniazid prophylaxis in patients with systemic lupus erythematosus receiving long term steroid treatment. *Ann Rheum Dis* 2002;61:251-3.
11. **Agrawal PN, Gupta D, Aggarwal AN, Behera D.** Incidence of tuberculosis among patients receiving treatment with oral corticosteroids. *J Assoc Physicians India* 2000;48:881-4.
12. **Hanta I, Ozbek S, Kuleci S, Seydaoglu G, Ozyilmaz E.** Detection of latent tuberculosis infection in rheumatologic diseases before anti-TNF therapy: tuberculin skin test versus interferon gamma assay. *Rheumatol Int.* 2012 Nov; 32(11):3599-605.
13. **Tam LS, Li EK, Wong SM, Szeto CC.** Risk factors and clinical features for tuberculosis among patients with systemic lupus erythematosus in Hong Kong. *Scand J Rheumatol* 2002;31:296-300.
14. **Balakrishnan C, Mangat G, Mittal G, Joshi VR.** Tuberculosis in patients with systemic lupus erythematosus. *J Assoc Physicians India* 1998;46:682-3.
15. **Cowrie RL, Sharpe JW.** Extra- pulmonary tuberculosis: a high frequency in the absence of HIV infection. *Int J Tuberc Lung Dis.* 1997 Apr;1(2):159-62.
16. **Tuberculous arthritis revisited as a forgotten cause of monoarthritis.** *Ann Saudi Med.* 2011 Jul- Aug; 31(4): 398- 401.
17. **Rajalingham S, Said MS, Shaharir SS, Abaziz A, Periyasamy P, Anshar FM.** Dermatomyositis masquerading musculoskeletal tuberculosis. *BMJ Case Rep.* 2011 Oct 28; 2011.
18. **Yoshida Y, Nakayama J, Furue M, Matsuda T.** Dermatomyositis with tuberculous fasciitis. *Eur J Dermatol.* 2004 Mar- Apr; 14 (2): 123- 124.
19. **Marie I, Menard JF, Hachulla E, Cherin P, Benveniste O, Tiev K, Hatron PY.** Infectious complications in polymyositis and dermatomyositis: a series of 279 patients. *Semin Arthritis Rheum.* 2011 Aug; 41 (1): 48- 60.
20. **Liu CH, Liu WC, Chen LW, Chen JS.** Tuberculous myofascitis in dermatomyositis. *Clinical Rheumatology.* June 2008. 27:7- 9.
21. **Camus JP, Koegeer AC, Nahoul K, Alcaix D, Gutmann L.** Isolated muscular tuberculosis in dermatomyositis treated with corticosteroids. Developing outbreak of dermatomyositis under rifampicin treatment: a report of 2 cases. *Ann Med Interne (Paris).* 1987; 138 (7): 524-6.
22. **Feng PH and Tan TH.** Tuberculosis in patients with systemic lupus erythematosus. *Annals of the Rheumatic Diseases,* 1982, 41, 11-14
23. **Victorio- Navarra ST, Dy EE, Arroyo C, Torralba T.** Tuberculosis among Filipino patients with systemic lupus erythematosus. *Seminars in Arthritis and Rheumatism* Vol 25 No. 3 December 1996: 628- 634.
24. **Punnonen R, Kiilholma P, Meurman L.** Female genital tuberculosis and consequent infertility. *Int J Fertil.* 1983;28:235-8.
25. **R.B.P. Thangappah, C.N. Paramasivan,* and Sujatha Narayanan*** Evaluating PCR, culture & histopathology in the diagnosis of female genital tuberculosis. *Indian J Med Res.* 2011 July; 134(1): 40-46.
23. **Chen IJ, Tsai WP, Wu YJ, Luo SF, Ho HH, Liou LB, Chen JY, Kuo CF, Chang HC, Yang CH, Yu KH.** Infections in polymyositis and dermatomyositis: analysis of 192 cases. *Rheumatology* 2010; 49: 2429-2437.
26. **Hassan, FOA.** Tuberculous dactylitis pseudotumor of an adult thumb: a case report. *Strat Traum Limb Recon* (2010) 5:53-56
27. **Andronikou S, Smith B.** “Spina ventosa” tuberculous dactylitis. *Arch Dis Child* 2002; 86(3):206
28. **Umansky AL, Schlesinger PT, Greenberg BB.** Tuberculous dactylitis in the adult. *Arch Surg.* 1947;54(1):67-78
29. **Poppel MH, Lawrence, LR, Jacobson HG, and Stein J.** Skeletal tuberculosis: roentgenographic survey with reconsideration of diagnostic criteria. *Am J Roentgenol, Rad Therapy & Nuclear Med* 1953; 70:936-963.
30. **Nathanson L, and Cohen, W.** Statistical and roentgenological analysis of 200 cases of bone and joint tuberculosis. *Radiology* 1941; 36: 550-567
31. **Feldman F, Auerbach R, and Johnston A.** Tuberculosis dactylitis in the adult. *Am J of Roentgenol* 1971;112: 460-479.
30. **Solovic I, Jonsson J, Korzeniewska- Kosela M, Chiotan DI, Pace-Asciak A, Slump E, Rumetshofer R, Abubakar I, Kos S, Svetina-Sorli P, Haas W, Bauer T, Sandgren A, van der Werf MJ.** Challenges in diagnosing extrapulmonary tuberculosis in the European Union, 2011. *Euro Surveill.* 2013;18(12):pii=20432. Available online: [http:// www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20432](http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20432).