CASE REPORT

Oropharyngeal Syphilis: Imaging and Pathologic Findings in Two Patients

Enric Ripoll¹ · Carla Montironi² · Lluïcia Alós² · Teresa Pujol¹ · Joan Berenguer¹ · Laura Oleaga¹

Received: 30 May 2016 / Accepted: 23 September 2016 / Published online: 3 October 2016
© Springer Science+Business Media New York 2016

Abstract Syphilis is a widespread infection with increasing frequency in developed countries, especially among men who have sex with men. We present two cases of oropharyngeal syphilis in two middle-aged men who presented with a painless tonsillar ulcer and progressive enlargement of cervical lymph nodes suspected of being a tonsillar tumour. A pathologic analysis of the ulcer led to an accurate diagnosis. We review the imaging and pathologic findings to emphasize the importance of taking syphilis into account in the differential diagnosis.

Keywords Syphilis · Cervical lymph node · Tonsillar tumour

Introduction

Syphilis is a sexually transmitted infection caused by *Treponema pallidum* and is still a common infection worldwide. The twenty first century has seen an increase in syphilis in populations of men who have sex with men, especially those infected with HIV [1–6].

Primary syphilis develops weeks after initial exposure, with a chancre appearing at the site of inoculation. This lesion starts as a papule and evolves into a painless ulcer,

accompanied by enlarged, non-tender, regional lymph nodes. The chancre usually arises in external genitalia but can appear in other less common sites such as anus, rectum, perineum, oropharynx, lips and hands [1, 7].

Chancres located in atypical sites such as the oropharynx are difficult to diagnose as they are painless and can remain unnoticed by the patient [3, 7]. In these cases the development of enlarged painless lymph nodes can be mistaken for a neoplasm [4, 8–10].

We report two cases of oropharyngeal syphilis in two middle-aged men with a painless tonsillar ulcer and progressive enlargement of cervical lymph nodes. Both were suspected of having a tonsillar tumour (carcinoma or lymphoma) with nodal involvement.

Biopsy and imaging studies were performed in order to diagnose and stage the disease. We review imaging and pathologic findings of these patients showing that oropharyngeal syphilis must be included in the differential diagnosis of a tonsillar tumour with lymph node involvement.

Case 1

A 47-year-old man presented with 6-weeks of progressive enlargement and non-tender right cervical lymph nodes. He denied experiencing fever, oropharyngeal or constitutional symptoms. Physical examination revealed enlarged right cervical lymph nodes and a small ulcer in the right tonsillar fossa (previous tonsillectomy). Endoscopy showed enlargement of the tongue base and right glosso-epiglottic fold. He was suspected of having a tonsillar carcinoma or lymphoma with lymph node involvement. Contrast enhanced neck CT (Fig. 1a–c) depicted the enlargement of the right tonsillar fossa, tongue base, and right glosso-epiglottic fold, with multiple enlarged right cervical lymph

✉ Enric Ripoll
enricripoll@hotmail.com
Carla Montironi
MONTIRONI@clinic.cat

¹ Radiology Department, Hospital Clínic de Barcelona, Villarroel 170, Barcelona, Spain

² Pathology Department, Hospital Clínic de Barcelona, Villarroel 170, Barcelona, Spain

Fig. 1 A 47-year-old man with 6 weeks of progressive enlargement of non-tender right cervical lymph nodes. Contrast enhanced CT of the neck (**a–c**): **a** Axial image shows enlargement of right tonsillar fossa (*wide arrows*) and two enlarged right cervical lymph nodes (*arrows*) with cystic changes consistent with central necrosis. **b** Right parasagittal image shows enlargement of tongue base (*wide arrows*). **c** Coronal image shows multiple right cervical lymph nodes with central necrosis (*arrows*). Histology of the tonsillar fossa and the lymph node (**d–k**): **d** (H&E; $\times 40$) Notice the ulceration of the mucosa (*wide arrow*) with abundant plasma cell infiltration (H&E;

$\times 200$) in **e**. Immunohistochemistry **f** reveals multiple treponema-type spirochetes (*wide arrow*; *Treponema pallidum* -Spirochetes-, Biocare Medical, Concord, CA; $\times 400$). **g** (H&E; $\times 1$) The lymph node shows a marked broadening of the capsule by chronic inflammation and fibrosis (*wide arrow*). **h** (H&E; $\times 100$) There is an outstanding infiltration of plasma cells, **i** (H&E; $\times 100$) isolated giant cells (“naked giant cells”, see *wide arrow*), **j** (H&E; $\times 100$) microgranulomas (*wide arrow*), as well as **k** (H&E; $\times 100$) perivascular lymphoplasmacytic infiltrate

nodes, one of which had cystic appearance consistent with central necrosis.

A biopsy was taken from the right tonsillar fossa and intraoperative frozen sections were performed. They were composed of multiple fragments that measured 1.2 cm

altogether. The diagnosis of epithelial neoplasia was ruled out and a reactive process was suggested. The paraffin-embedded tissue sections showed an epithelial ulceration (Fig. 1d) and chronic inflammation with a remarkable number of plasma cells (Fig. 1e). No alteration in the

lymphoid population immunophenotype was seen using CD3, CD5, CD20, and CD79a antibodies. The immunostain for *Treponema pallidum* antibody demonstrated a large number of spirochetes in the tonsillar tissue (Fig. 1f).

An enlarged cervical lymph node was also removed. Under microscopic examination, it exhibited an effaced architecture due to accentuated cortical and paracortical hyperplasia (Fig. 1g). It had a marked broadening of the capsule by fibrosis and chronic inflammation and an outstanding abundance of plasma cells (Fig. 1h). There were isolated multinucleated giant cells (Fig. 1i) and few small non-caseating epithelioid granulomas (Fig. 1j) among the lymphocytes of the parenchyma. A perivascular lymphoplasmacytic infiltrate was seen in small vessels of the lymph node (Fig. 1k). The immunohistochemistry study using CD3, CD5, CD20, CD79a, BCL-6, CD10, CD23, CD21, BCL-2, and light chains kappa and lambda antibodies confirmed a reactive etiology and ruled out lymphoma. *In situ* hybridization for Epstein Barr virus, PAS, and Zielh Nielsen stains were all negative.

A final diagnosis of syphilitic ulcer in the tonsillar fossa and luetic lymphadenitis was made.

Only after CT and biopsy were performed did the patient develop penile lesions consistent with condyloma lata (a typical cutaneous manifestation of secondary syphilis). Serologic tests (treponemal and non-treponemal) were positive and HIV serology was negative. He was treated with penicillin with satisfactory results.

Case 2

A 42-year-old man presented with 2 months of sore throat and progressive enlargement of non-tender left cervical lymph nodes. He had slight malaise and hyporexia, but no fever. He had a recent history of HIV infection that was still untreated, with a normal CD4 blood count. Physical examination confirmed an enlargement of left cervical lymph nodes with an ulcer in the left tonsil. Endoscopy revealed enlargement of the left side of the pharynx with no other findings. He was also suspected of having a tonsillar tumour (either carcinoma or lymphoma) with lymph node involvement. Neck MR (Fig. 2a–c) showed bilateral tonsillar enlargement (with left predominance), enlargement of left side of pharynx and occupation of left pyriform sinus. Multiple bilateral enlarged lymph nodes were identified, some of which had central cystic changes consistent with necrosis.

Tonsillar biopsies were obtained, showing a widely ulcerated mucosa with an abundant infiltrate of plasma cells (Fig. 2d, e). There was also a mixed infiltrate with neutrophils, karyorrhexis and apoptotic bodies. Vessels had a reactive appearance with tall endothelium and some displayed luminal obliteration (Fig. 2f). In order to rule out

a lymphoma, immunohistochemistry was performed, showing a reactive lymphoid model with abundant CD138 positive plasma cells. *In situ* hybridization for Epstein Barr virus was also negative in this case. The immunohistochemistry for *Treponema pallidum* antibody showed a large number of spirochetes and a diagnosis of syphilitic ulcer was made (Fig. 2g, h).

Again, only after CT and biopsy had been performed did the patient develop cutaneous manifestation of secondary syphilis (in this case, a diffuse maculopapular rash with palm involvement). Serological tests for syphilis (VDRL, IgM and IgG) and PCR for *T. pallidum* in tonsillar ulcer were positive. He was treated with penicillin with resolution of the symptoms.

Discussion

Syphilis is a re-emergent infection in developed countries. Men who have sex with men, especially those infected with HIV, are the group with highest risk of infection [1–4, 6] and where the highest frequency of extragenital location of primary syphilis has been observed [1, 7].

Oropharyngeal syphilis is difficult to diagnose because chancre usually goes unnoticed and so when local lymphadenopathies arise they appear to mimic neoplasms [4, 9]. Because of the general sensitivity to cancer and the need of a rapid diagnosis to initiate treatment, oropharyngeal syphilis can be imaged and biopsied weeks before symptoms of secondary syphilis appear. There are several cases described in the literature of oropharyngeal syphilis being initially misdiagnosed as a neoplasm [4, 8–15].

Unfortunately, imaging findings in oropharyngeal syphilis are non-specific [13–15]. Previously published cases with imaging studies have reported asymmetric tonsillar enlargement with enlarged bilateral cervical lymph nodes [4, 9–18]. One previous case report described cystic nodal changes (as in our two cases) but they attributed this finding to previous antibiotic treatment [17]. Nodal and tonsillar increased contrast enhancement and ¹⁸F-FDG-uptake have also been described for CT [14], MR [13], and PET-CT [12, 16].

Pathological diagnosis of these cases is also difficult where syphilis is not clinically suspected and lesions are submitted as carcinoma or lymphoma.

In addition, it may be difficult to define inflammation histologically because tonsils are mucosa-associated lymphoid tissue and the continuous antigenic stimulation of the tonsils has been termed as “physiologic inflammation”. Lymphocytes are seen normally in the epithelium but the presence of neutrophils indicates acute mucositis. The infiltration by plasma cells is not specific but characterizes all stages of syphilis.

Fig. 2 42-year-old man with 2 months of sore throat and progressive enlargement of non-tender left cervical lymph nodes. MR of the neck (**a–c**). Axial T1 fat-saturation post-gadolinium sequences: **a** Enlargement of both tonsils with left predominance (wide arrows) and bilateral enlarged lymph nodes (arrows). **b** Irregular enlargement with hyperenhancement of left pharyngeal wall (arrowhead) and enlarged lymph nodes (arrows), one of which had a hypoenhancing centre consistent with cystic changes due to central necrosis. **c** Occupation and hyperenhancement of left pyriform sinus (arrowhead) and

enlarged lymph nodes (arrows). Biopsies of the tonsil (**d–h**): **d** (H&E; ×40) Mucosal ulceration: there is no surface epithelium (wide arrow). **e** (H&E; ×100) Plasma cell infiltrate with **f** (H&E; ×400) obliteration of small vessels because of reactive endothelium (wide arrow). **g** and **h** (*Treponema pallidum* -Spirochetes-, Biocare Medical; ×400) Immunohistochemistry shows multiple treponemate-type spirochetes (wide arrow) **h** (*Treponema pallidum* -Spirochetes-, Biocare Medical; ×200) localized around the vessels (wide arrow)

In primary syphilis, the overlying squamous epithelium is thin and eventually ulcerates. Lymphoplasmacytic vasculitis with a ‘coat sleeve’-like arrangement, endothelial proliferation and lymphoplasmacytic neuritis can be seen, although were not found in our cases. Immunohistochemistry with commercial polyclonal antibody for *Treponema pallidum* is more sensitive than silver stain and can be used

on paraffin-embedded tissue. It can reveal spirochetes that are more frequently seen around vessels but can also be localized in the squamous epithelium or in the submucosa. Polymerase chain reaction may be helpful in immunohistochemical negative studies.

In secondary syphilis, a granulomatous reaction with Langerhan’s multinucleated cells can be found and

spirochetes can be seen, mostly around vessels. However, plasma cells may be scant. The diagnosis of syphilis should be considered in any mucosal lesion with a plasmacytic infiltrate, although infiltrate may be limited.

The draining lymph node may present reactive changes with numerous plasma cells associated with marked follicular hyperplasia that can resemble a lymphoma, which can be ruled out by immunohistochemical studies. In our first case there was an effacement of the architecture of the lymph node and a broadening of the capsule by chronic inflammation, which is typical of syphilitic lymphadenitis. Nodal pattern of a reactive entity was revealed by immunophenotypical study. Perivascular cuffs of plasma cells and lymphocytes can be seen in vessels of the capsule and pericapsular tissue. In both our cases there was a prominent plasma cell proliferation. Noncaseating microgranulomas were also found, as well as completely isolated multinucleated giant cells, which are called ‘naked giant cells’. None of these findings are specific to syphilis and may go unnoticed without a careful analysis.

In conclusion, these two cases show that primary syphilis is an important candidate in the differential diagnosis of cancer in the neck region because of its clinical presentation and increasing frequency [19]. Imaging findings are non-specific and pathologic diagnosis is not straightforward. Clinicians, radiologists, and pathologists must be aware of these facts as they may have to consider them within the context of suspected neoplasm.

Compliance with Ethical Standards

Conflict of interest No conflict of interest to disclose.

References

- Cohen SE, Klausner JD, Engelman J, et al. Syphilis in the modern era: an update for physicians. *Infect Dis Clin N Am*. 2013;27(4):705–22.
- Shockman S, Buescher LS, Stone SP. Syphilis in the United States. *Clin Dermatol*. 2014;32(2):213–8.
- Fiumara NJ, Walker EA. Primary syphilis of the tonsil. *Arch Otolaryngol*. 1982;108(1):43–4.
- Jang DW, Khan A, Genden EM, et al. Syphilitic lymphadenitis diagnosed via fine needle aspiration biopsy. *Diagn Cytopathol*. 2011;39(8):603–5.
- Morshed MG. Current trend on syphilis diagnosis: issues and challenges. *Adv Exp Med Biol*. 2014;808:51–64.
- Patton ME, Su JR, Nelson R, et al. Primary and secondary syphilis: United States, 2005–2013. *MMWR Morb Mortal Wkly Rep*. 2014;63(18):402–6.
- Bruce IA, Roper AJ, Gayed SL, et al. Syphilitic cervical lymphadenopathy: return of an old foe. *Am J Otolaryngol*. 2009;30(5):347–9.
- Ikenberg K, Springer E, Bräuninger W, et al. Oropharyngeal lesions and cervical lymphadenopathy: syphilis is a differential diagnosis that is still relevant. *J Clin Pathol*. 2010;63(8):731–6.
- Yuan Y, Zhang X, Xu N, et al. Clinical and pathologic diagnosis and different diagnosis of syphilis cervical lymphadenitis. *Int J Clin Exp Pathol*. 2015;8(10):13635–8.
- Hamlyn E, Marriott D, Gallagher RM. Secondary syphilis presenting as tonsillitis in three patients. *J Laryngol Otol*. 2006;120(7):602–4.
- Oddó D, Carrasco G, Capdeville F, et al. Syphilitic tonsillitis presenting as an ulcerated tonsillar tumor with ipsilateral lymphadenopathy. *Ann Diagn Pathol*. 2007;11(5):353–7.
- Fu Z, Zhang J, Li Q, Liu M, et al. A case of secondary syphilis involving tonsil, pulmonary, and multiple lymph nodes: 18F-FDG PET/CT findings. *Clin Nucl Med*. 2015;40(4):335–7.
- Pan X, Zhu X, Li QQ. Syphilis manifesting as a nasopharyngeal carcinoma with cervical lymphadenopathy: a case report. *Exp Ther Med*. 2012;3(6):1023–5.
- Sato J, Tsubota H, Himi T. Syphilitic cervical lymphadenopathy. *Eur Arch Otorhinolaryngol*. 2003;260(5):283–5.
- Wang X, Li WQ, Liu HM, et al. Isolated syphilitic cervical lymphadenopathy: report of two cases and review of the literature. *J Int Med Res*. 2012;40(5):1988–2000.
- Kim JM, Lee SM, Bae SB, et al. The role of PET/CT in diagnosing generalized lymphadenopathy in asymptomatic secondary syphilis. *Hell J Nucl Med*. 2016;19(1):60–2.
- Shimizu T, Shinogi J, Majima Y, et al. Secondary syphilis of the tonsil. *Arch Otorhinolaryngol*. 1989;246:117.
- Barbee LA, Centor RM, Goldberger ZD, et al. Clinical problem-solving. A history lesson. *N Engl J Med*. 2015;372(14):1360–4.
- Yarington CT Jr, Jensen OC. Syphilis as a differential diagnosis of neck masses. *Arch Otolaryngol*. 1967;86(2):219–21.