

[CASE REPORT]

Syphilitic Cervicitis with Cervical Cancer Presenting as Oropharyngeal Syphilis

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Abstract:

We herein report a patient with syphilitic cervicitis and cervical cancer presenting as oropharyngeal syphilis. A 31-year-old Japanese woman with a history of unprotected vaginal and oral sex visited our hospital with right submandibular adenomas and erythema in the extremities. The fornix uteri was red, with a nodule noted. The rapid plasma reagin ratio was 1:3. She was diagnosed with syphilitic cervicitis and treated with amoxicillin for four weeks. Initial cervical cytology showed cells with mild nuclear enlargement, which was thought to be metaplasia associated with syphilis. Repeated cytology a month later showed a high-grade squamous intraepithelial lesion. A punch biopsy of the lesion led to the pathological diagnosis of cervical carcinoma *in situ*. We performed cervical conization, and no recurrence occurred. Human papillomavirus (HPV) immunostaining was positive in the lesion. Mucosal lesions are an infrequently reported symptom of syphilis. When oropharyngeal lesions are found, the sexual history should be ascertained, and the patient should be screened for sexually transmitted diseases. HPV is especially significant because of its association with cervical cancer. Coinfection of HPV with cervical cancer must be ruled out during follow-up for women when oropharyngeal syphilis involves genital lesions.

Key words: uterine cervicitis, syphilis, uterine cervical neoplasms

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Introduction

We encountered a patient with syphilitic cervicitis complicated with cervical cancer that presented as oropharyngeal syphilis with erythema. Such a presentation has rarely been reported. Syphilis, a sexually transmitted disease caused by *Treponema pallidum*, has seen a recent worldwide resurgence (1, 2). In Japan, the number of patients with syphilis was below 1,000 in 2012 but had increased to over 5,000 by 2017 (3). Syphilis is often asymptomatic, and screening is recommended for people at risk of sexually transmitted diseases. Oropharyngeal syphilis, seen in our patient, rarely occurs, but when it does, it is most often seen in cases of secondary syphilis. It is highly contagious but sometimes difficult to diagnose, as in the present patient, so the early detection and treatment in primary care is necessary in order to prevent the spread of infection (4).

Case Report

A 31-year-old Japanese woman visited our hospital with a 2-month history of right submandibular adenoma. She had also noticed erythema in her extremities two weeks before presentation. She had previously visited the dentist and the otolaryngologist, at which point she had been prescribed antihistamine agents without a confirmatory diagnosis. She worked as a commercial sex worker (CSW) with a history of unprotected sexual intercourse with many partners. A further history taking revealed repeated experiences with unprotected oral sex. She had undergone Pap smear a year before the presentation but never received a human papillomavirus (HPV) vaccination.

On a physical examination, her general appearance was alert and oriented with no acute distress. Her temperature was 36.5°C, pulse rate 107 beats per minute, blood pressure 122/76 mmHg, and respiratory rate 12 breaths per minute.

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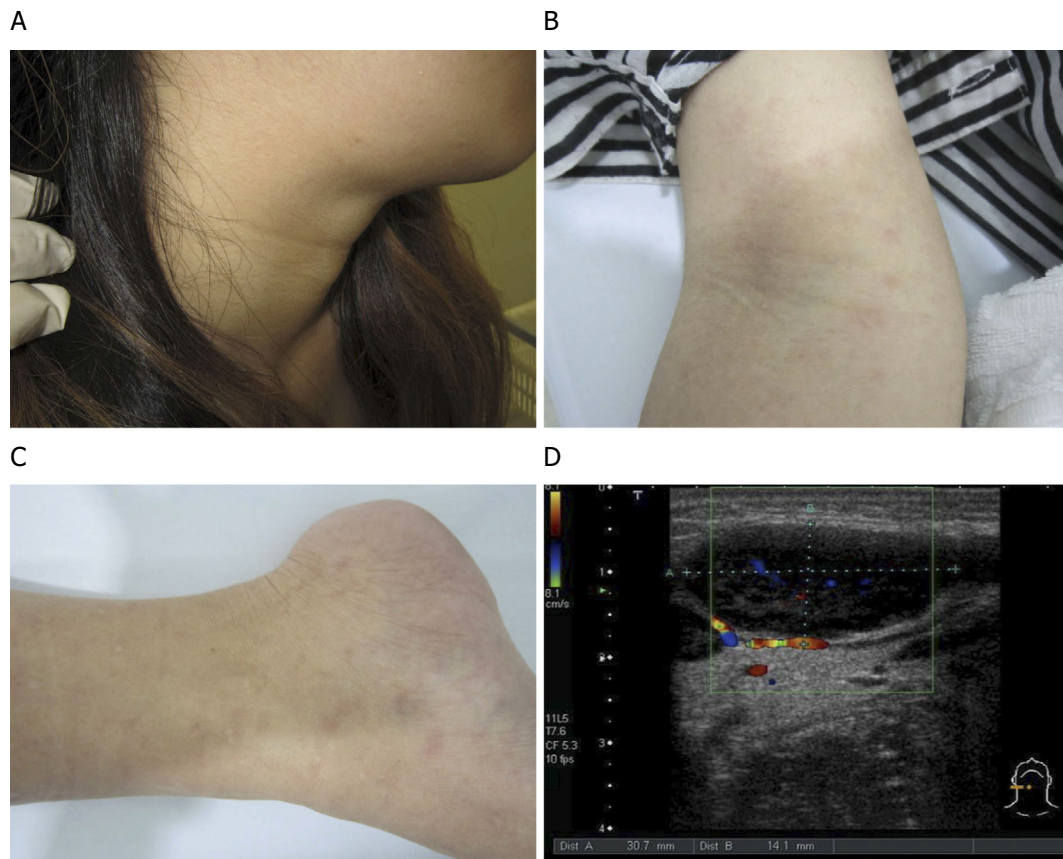


Figure 1. The right superficial neck lymph node was engorged by approximately 3 cm without tenderness (A). Multiple erythema are seen in both limbs (B, C). An ultrasound examination of the cervical lymph node revealed multiple lymphadenopathy in both cervical areas, including a 30×14 mm lymphadenopathy in the right anterior cervical region (D).

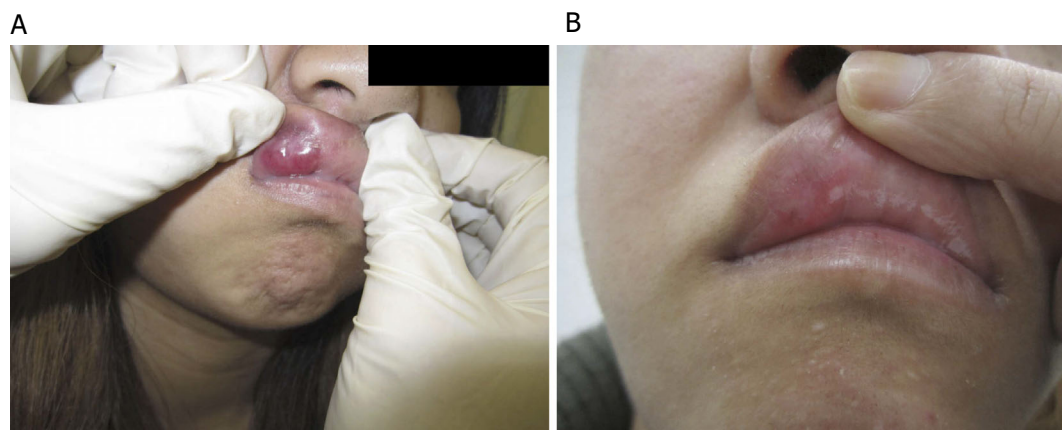


Figure 2. An induration was observed on the right upper lip (A). Oral lesions disappeared after amoxicillin therapy (B).

The right superficial neck lymph node was engorged by approximately 3 cm without tenderness (Fig. 1A). A painless induration was observed on the right upper lip (Fig. 2A). Multiple erythema had appeared on the bilateral upper and lower extremities (Fig. 1B and C). Since she was a CSW with a history of unprotected sexual intercourse with many partners, we performed a pelvic examination to examine her for sexually transmitted infections. Chancres were apparent

on both labia majora. The fornix uteri was red and inflamed with a nodule. Findings on cardiac, respiratory, abdominal, neurologic, and musculoskeletal examinations were normal. An ultrasound examination of the cervical lymph node revealed multiple lymphadenopathy on both sides, including 30×14 mm lymphadenopathy in the right anterior cervical region (Fig. 1D). No increase in the blood flow was observed in the lymph nodes.

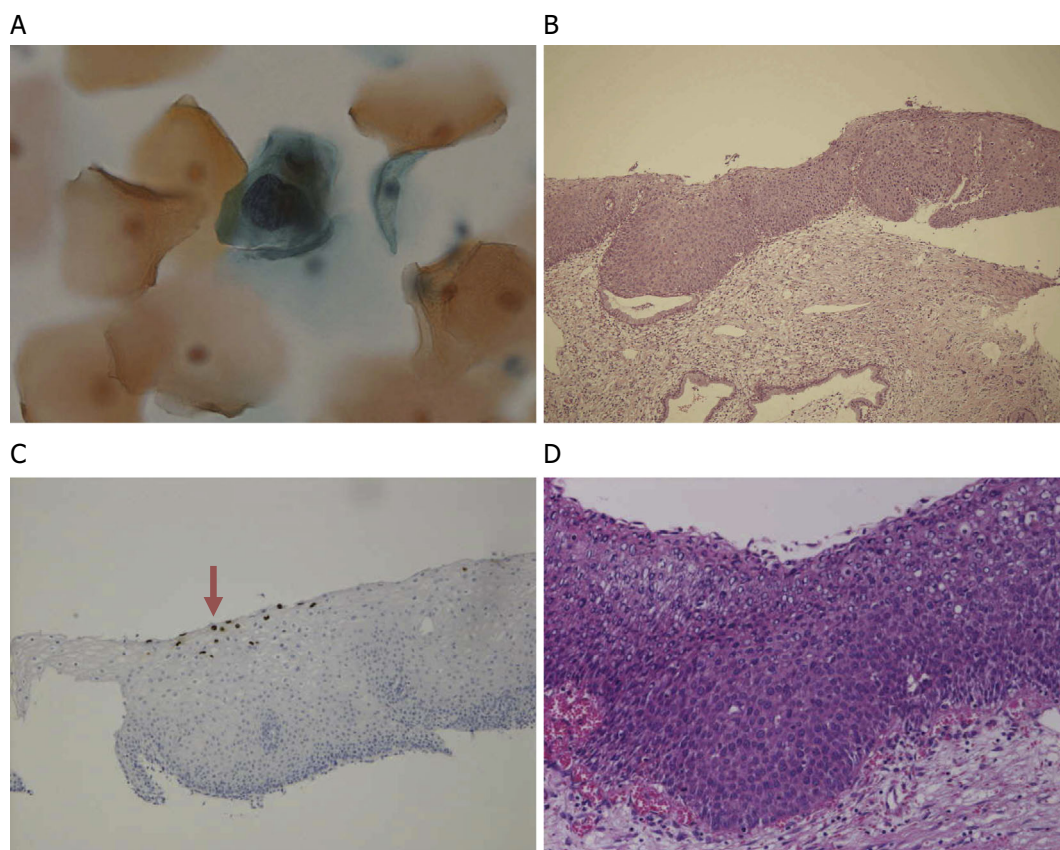


Figure 3. Follow-up cervical cytology four weeks after presentation revealed a high-grade squamous intraepithelial lesion (A). A punch biopsy specimen obtained from the squamocolumnar junction area showed inflammatory cell infiltration and atypical cell proliferation of the epithelial layer, resulting in a histopathological diagnosis of cervicitis and carcinoma *in situ* (B). HPV immuno-staining was positive in the epithelial lesion (red arrow) (C). The conization specimen was diagnosed as cervical intraepithelial neoplasia 3 (severe dysplasia/cervical carcinoma *in situ*) with ductal progression (D).

A laboratory examination revealed elevated C-reactive protein levels (1.0 mg/dL), normal white blood cell counts (5,890/ μ L) and 70% neutrophils (normal range: 42-77%). The levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were normal at 11 IU/L and 7 IU/L (normal range: 8-38 IU/L and 4-44 IU/L), respectively. The level of lactate dehydrogenase (LDH) was normal at 129 IU/L (normal range: 106-211 IU/L). The level of creatinine phosphokinase (CPK) was not elevated at 23 IU/L (normal range: 25-170 IU/L). A *Treponema pallidum* particle agglutination assay (TPPA) was positive, and the rapid plasma reagin (RPR) ratio was 1:3. Polymerase chain reaction tests of the cervical swab sample against *Neisseria gonorrhoeae* and *Chlamydia trachomatis* were negative. Findings from an antigen test for hepatitis B surface and antibody tests for hepatitis C virus and human immunodeficiency virus were also negative.

Syphilitic cervicitis was diagnosed, and she was treated with 1.5 g of amoxicillin per day for 4 weeks according to the guidelines by the Japanese Society for Sexually Transmitted Infections (5). The erythema and oral and genital lesions disappeared (Fig. 2B). The RPR ratio increased again

to 1:74 at 1 week after treatment but became negative after therapy. Initial cervical cytology revealed cells with mild nuclear enlargement. Although this was thought to be metaplasia associated with syphilis, follow-up cervical cytology four weeks after presentation revealed a high-grade squamous intraepithelial lesion (Fig. 3A). A punch biopsy specimen obtained from the squamocolumnar junction area showed inflammatory cell infiltration and atypical cell proliferation of the epithelial layer, which resulted in a histopathological diagnosis of cervicitis and carcinoma *in situ* (Fig. 3B). HPV immuno-staining was positive in the epithelial lesion (Fig. 3C).

We performed cervical conization and no recurrence occurred. The conization specimen was diagnosed as cervical intraepithelial neoplasia 3 (severe dysplasia/cervical carcinoma *in situ*) with ductal progression. No interstitial infiltration was identified (Fig. 3D). The patient quit working as a CSW.

Discussion

Syphilis, dubbed “the great imitator” due to its exhibition

Table 1. Phases of Oropharyngeal Lesions of Syphilis (7).

Primary	primary induration, hard chancre, painless lymphadenopathy lips are more commonly affected
Secondary	mucous patches, leukoplakia like plaque, multiple and painful
Tertiary	gummas

Table 2. Summary of Published Reports of Cervical Syphilitic Lesions Mimicking Cervical Cancer.

Reference	Age	Initial diagnosis	Cytologic finding	Pathological diagnosis of cervical biopsy
(12)	21	Sarcoma of the uterus	None	Chronic inflammation →Complete resolution after three months
(13)	42	Cervical cancer	Acute and chronic inflammation	Severe chronic cervicitis (after four weeks)
(13)	46	Invasive cervical cancer	Negative	Granulomatous inflammation (after two weeks)
(14)	42	Cervical cancer	None	Chronic inflammation →Normal cervix after three months
This case	31	Syphilis	HSIL	CIN3 (after two months)

HSIL: high-grade squamous intraepithelial lesion, CIN: cervical intraepithelial neoplasm

of various symptoms, requires treatment from a wide variety of specialties, so comprehensive management is the cornerstone of patient care (6). The most prevalent, classic course of syphilis is as follows in descending order: rash (81-100%), lymphadenopathy (70-86%) and mucosal lesion (7-56%) (7). When oropharyngeal lesions such as induration or vitiligo are found, the patient's sexual history should be ascertained, and sexually transmitted diseases should be screened.

We classify the present patient's syphilitic oropharyngeal lesions in Table 1 according to the reports by Strieder et al. (8) and Aarestrup et al. (9). Hard chancre and primary induration are characteristic lesions of primary syphilis (8). The lesions rarely occur in the mouth, but when they do, the lips are the most commonly affected site. Primary chancres are typically painless and disappear within four to five weeks (8). They often accompany ipsilateral lymphadenopathy, which is also painless. Without treatment for the disease, however, up to 90% of patients with primary syphilis will advance to the secondary stage (4). Oral lesions of secondary syphilis are typically multiple and painful, commonly called "mucous patches" and "leukoplakia-like plaque" (10). Lesions in the upper lip are more common in men, whereas those in the lower lip are more common in women (8). Our patient also had a painless primary induration on her upper lip, but this appears to be different from the mucous patches associated with secondary syphilis. Approximately one-third of untreated patients develop tertiary syphilis, and its characteristic sign is the inclusion of gummas (4).

The presently reported patient had typical oropharyngeal features of primary syphilis: she had noticed submandibular

enlargement two months previously, which might indicate a two-month history of primary induration on the lip and painless ipsilateral lymphadenopathy. The patient also developed erythema in her extremities, another manifestation of secondary syphilis, two weeks before presentation. The timeline of symptoms matched the course of syphilis. Case findings based on primary oropharyngeal features may help contribute to the early detection and prevention of transmission of the disease.

The RPR ratio was relatively low at this patient's first measurement. This may have been due to the prozone phenomenon, which occurs when the RPR ratio is very high and causes interference with the clumping of antigen-antibody complexes. This phenomenon is particularly common in patients with secondary syphilis and in pregnant women (11).

Table 2 summarizes the published reports of cervical syphilitic lesions mimicking cervical cancer (12-14). Among the four reported patients, three were diagnosed with cervical cancer and one with sarcoma of the cervix. A pathological examination of cervical biopsy specimens revealed inflammation in all patients. Two patients were confirmed to be completely recovered based on the findings of a re-biopsy. The present patient was initially thought to have syphilis, but repeated cervical smear tests and cervical biopsies led to the final diagnosis of syphilitic cervicitis with cervical cancer.

Reports of syphilitic cervicitis are rare, and there are few reports of complication with cervical cancer. Distinguishing it from cervical cancer is difficult, so ongoing patient care, including a re-examination with cervical cytology, is key to the diagnosis. Furthermore, an encounter with syphilis war-

rants investigation of the possibility of other sexually transmitted infections. HPV infection is particularly significant because of its commonality and link to cancer. We should consider the possibility of coinfection with HPV with other sexually transmitted infections. In Japan, free vaccination against HPV was made available in December 2010; however, the Japanese Ministry of Health, Labour and Welfare suspended proactive recommendations for the HPV vaccine after unconfirmed reports of adverse events following vaccination were reported in the media in June 2013 (15). The HPV vaccination rate has therefore significantly dropped in Japan (16). Despite 17 relevant Japanese academic societies recommending the promotion of the HPV vaccine, the routine vaccination in Japan has not yet been resumed (17). Without HPV vaccination, we will continue to encounter patients with conditions similar to that in the present report. Therefore, proactive promotion and recommendation of vaccination should be resumed.

In conclusion, coinfection of HPV and cervical cancer must be ruled out during follow-up for women with oropharyngeal syphilis involving genital lesions.

The authors state that they have no Conflict of Interest (COI).

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