

한국에서 비전형적 2기 매독의 임상적 특징

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Unusual Presentation of Secondary Syphilis in Korea: 2010-2014 Review

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The prevalence of syphilis differs according to the object and district. Diagnosis of syphilis remains challenging, as the absence of classical features of disease, such as the secondary syphilis orogenital lesion rash, might make accurate diagnosis difficult. However, recent studies have reported a growing prevalence of symptomatic syphilis in Korea. The main reason is the rise in primary and secondary syphilis. The most common clinical features of primary and secondary syphilis are orogenital lesions, masculopapular rash, and generalized lymphadenopathy. An increasing number of unusual clinical presentations have been reported among secondary syphilis cases. The aim of this study was to remind us of the significance of syphilis by highlighting the unusual clinical presentation of secondary syphilis.


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INTRODUCTION

Syphilis is a chronic sexually transmitted infection caused by *Treponema pallidum* subspecies *pallidum*. Due to the wide ranging variability in clinical presentation, the disease has earned the label “the great mimicker.”^{1,2} Clinical diagnosis is often missed or delayed because features can vary, and the diagnosis depends on the completeness of the clinical history and physician experience.^{2,3}

The prevalence of syphilis in Korea is increasing, and syphilis prevalence is generally under reported for cultural reasons. A recent report emphasized that the prevalence of primary and secondary syphilis is rising.¹ According to

the Korean Centers for Disease Control and Prevention, the number of primary syphilis cases per 100,000 was 1.36 per year and that for secondary syphilis was 0.46 per year in 2011.⁴ Considering the large portion of latent syphilis cases among the total number of syphilis cases, symptomatic syphilis must be treated aggressively to reduce the public health damage caused by syphilis.

Although several oral and rectal lesions represent an unusual clinical presentation by non-pathogenic *T. pallidum*, primary syphilis is usually detected by ulcerative lesions in the orogenital area.^{2,3} Secondary syphilis is characterized by multisystem involvement, including skin rash, condylomata lata, mucosal lesions, and generalized

lymphadenopathy. Secondary syphilis has diverse clinical presentations because it is hematogenously spread.³ Physicians often overlook its unusual presentation in an actual clinical setting.

In this brief review, we document the unusual presentations of secondary syphilis reported recently in Korea and discuss relevant issues together with cases from other countries.

MAIN SUBJECTS

1. Unusual Secondary Syphilis Presentation in Korea

Secondary syphilis is characterized by multisystem involvement, including skin rash, condylomata lata, mucosal lesions, and generalized lymphadenopathy. Secondary syphilis has diverse clinical presentations because it is hematogenously spread.³ Seven unusual clinical secondary syphilis presentations were reported during 2010-2014 (Table 1).

2. Bone Involvement

Bone and joint involvement in early syphilis is rare and more commonly seen in patients with congenital and tertiary syphilis.⁵ The availability of improved imaging modalities, such as computed tomography, magnetic resonance imaging, and bone scintigraphy scans, has led to easier diagnosis and more frequent reporting of osseous syphilis during the past decade. Although only one report about this issue has been documented in Korea,⁶ other similar reports are available from other countries.⁷⁻¹⁶

Bone pain is the most common complaint, which is aggravated during the night and upon exposure to heat and pressure. Involvement of the skull can lead to headache, usually in the frontotemporal area.⁶⁻¹⁶ Prompt resolution of bone pain after penicillin therapy is evidence of a syphilitic cause for the bone lesions. A diagnosis of early syphilis is suspected based on the mucocutaneous findings in 76% of patients. However, no history of primary or secondary syphilitic mucocutaneous lesions was found in 24% of the cases reviewed here, and high-titer nontreponemal serological tests were the only evidence of early syphilis in these patients.

3. Generalized Lymphadenopathy: Malignant Lymphoma mimicry

Lymphadenopathy is a common clinical finding with a broad differential diagnosis, including infectious disease, lymphoproliferative disorders, and autoimmune diseases.¹⁷ No other studies have been reported in other countries, except Park et al.¹⁸ in Korea. Positron emission tomography (PET) scans are commonly used to stage malignancies. However, fludeoxyglucose (FDG) uptake is not specific, as uptake is not only seen in organs but also occurs due to other nonneoplastic etiologies, such as inflammatory, reactive, or infectious causes.² No case of secondary syphilis with FDG-PET findings has been reported, except Park et al.¹⁸

4. Cholestatic Hepatitis and Thrombocytosis

Only one report on cholestatic hepatitis and thrombocytosis exists in Korea.¹⁹ The clinical manifestations of syphilitic hepatitis are likely to be subsequent to dissemination of treponema from the primary lesion site to the liver.^{20,21} A generalized rash and hepatomegaly are often present. Laboratory findings include a modest increase in transaminases and bilirubin but a marked increase in alkaline phosphatase and gamma-glutamyl transferase.²¹ While this cholestatic pattern is more typical, some cases show predominant hepatocellular damage.²² We found a predominant cholestatic pattern in our patient.

Reports of thrombocytosis accompanying secondary syphilis are uncommon and are mostly limited to neonatal patients. Platelet abnormalities in this setting are largely thrombocytopenia.²³ The presence of spirochetes in liver tissue is diagnostic but difficult to demonstrate. Treponemas are observed in about half of reported cases.²⁴⁻²⁶ Although one reported adult case developed fulminant hepatitis, most cases show complete clinical and laboratory recovery after treatment with benzathine penicillin G.²⁷

Although the mechanism of secondary syphilitic hepatitis has not been elucidated, anal intercourse between homosexual persons has been proposed as a risk factor, this behavior is thought to lead to *T. pallidum* in the portal circulation.

5. Nodular Skin Lesions

A presentation of nodular secondary syphilis is rare, with only a handful of reports, and lesions are typically described

Table 1. Unusual presentation of secondary syphilis in Korea

Author, year	Sex	Age (y)	Chief complaint	Clinical presentation	Orogenital lesion	Serologic marker (quantity)	Fluorescent treponemal antibody test/hemagglutination	Confirmation of <i>Treponema pallidum</i>	Remark
Park et al. 2014 ⁶	M	41	Back pain for 1 month Weight loss for 3 months	Maculopapular rash, including the palms and soles, in association with generalized lymphadenopathy	No	RPR 1:64	Positive	Not detected	MRI of the lumbar spine revealed bone destruction and extraskelatal soft tissue formation at the right side of the L5 vertebral body
Park et al. 2013 ¹⁸	M	45	Progressive weakness, hair loss, anorexia, 10-kg weight loss, and night sweats for 3 months	Non tender and freely movable bilateral inguinal lymph node was palpated.	Yes, one month ago	VDRL 1:32	Positive	Detected	CT revealed several enlarged lymph nodes in porta hepatitis; gastrohepatic, perigastric, aortocaval areas; splenic hilum; and mesenteric and both inguinal areas.
Kim et al. 2010 ¹⁹	M	42	Malaise and jaundice for one month	Icteric sclera and tender hepatomegaly macular and papular lesions, about 0.5 cm in diameter, localized on the trunk, palms, and soles	No	VDRL >1:1,024	Positive	Not detected	Mildly enlarged liver, nonspecifically enlarged lymph nodes at the porta hepatitis area, and thickened gall bladder wall
Jang et al. 2011 ³⁰	M	46	Raised skin lesion on his scalp for one month	Scalp lesion was a 1 × 1 cm single erythematous scaly nodule on the occiput	No	VDRL 1:128	Positive	Detected	Numerous spirochetes in the epidermis and at the dermoepidermal junction
Kim et al. 2013 ³⁷	M	51	Chest pain, fever, and myalgia for 2 weeks	Erythematous papular rash on the trunk, right cervical, and bilateral inguinal non tender, nonmovable lymphadenopathy was noted	Yes, 6 weeks earlier	VDRL 1:64	Positive	Not detected	CT scan showed multiple variably sized nodules in both lungs, suggesting the possibility of a hematogenous metastatic malignancy
Yoon et al. 2013 ⁴³	F	59	Speech disturbance for 20 days	Cognitive disturbance and dysarthria	Yes, 2 months earlier	VDRL 1:16	Positive	Not detected	First presentation was diagnosed as unknown brain tumor but secondary syphilis was diagnosed at secondary presentation
Jo et al. 2013 ⁴⁹	M	22	Recurrent oral ulcers, genital erosions for several months	Multiple elliptical crusted erosions are found on the scrotum. Crops of hyperpigmented tender nodules are located on both shins	Yes	Not mentioned	Positive	Detected	Initial diagnosis was Behçet's disease

M: male, F: female, RPR: rapid plasma reagin, VDRL: venereal disease research laboratory test, MRI: magnetic resonance imaging, CT: computed tomography.

as multiple red or purple nodules.²⁸ Nodular lesions are usually a manifestation of tertiary syphilis, but they have also been described in patients with secondary syphilis. Nodular eruption of secondary syphilis may be localized and tends to affect the face, mucous membranes, palms, and soles. Scaling may be present. The lesions typically do not form a specific pattern, although an annular configuration may be noted.^{3,28,29} The clinical features and histopathology of secondary and tertiary syphilis overlap, and distinguishing these two stages using standard diagnostic criteria is sometimes impossible.^{3,28,29} Nodular secondary syphilis is particularly important, as it may be a precursor to tertiary syphilis, which is a potentially morbid condition. Jang et al.³⁰ reported an unusual nodular lesion in the scalp area recently in Korea.

6. Pulmonary Nodules

Pulmonary involvement is well described in cases of congenital and tertiary syphilis.³¹ However, pulmonary involvement is extremely rare in patients with secondary syphilis. Nine cases of pulmonary involvement in patients with secondary syphilis have been reported since 1966.² Pulmonary lesions appear as an infiltration,³ consolidation with pleural effusion,³² solitary pulmonary nodule,³³ or multiple ill-defined nodules.³⁴ Kim et al.³⁵ reported the third case of secondary syphilis, presenting as multiple pulmonary nodules, and this was the first report in Korea. The importance of this issue is that well-defined pulmonary nodules could mimic hematogenous metastatic carcinoma.

7. Cerebral Syphilitic Gumma: Brain Tumor Mimicry

The central nervous system (CNS) is involved in 5-10% of untreated patients at any stage of syphilis infection.³⁶ CNS involvement in patients with syphilis is classified into four syndromes, such as syphilitic meningitis, meningo-vascular syphilis, and parenchymatous and gummatous neurosyphilis. Distinguishing a brain mass in an human immunodeficiency virus (HIV)-negative patient with syphilis is challenging to clinicians.³⁷⁻⁴⁰ Yoon et al.⁴¹ reported an unusual case of cerebral syphilitic gumma mimicking a brain tumor with relapse of secondary syphilis in a HIV-negative patient that was successfully controlled by administering ceftriaxone.

8. Nodular Vasculitis

Skin lesions in patients with syphilis commonly mimic those of other diseases, such as malignancy, sarcoidosis, inflammatory bowel disease, and Behçet's disease.⁴²⁻⁴⁵ Although cutaneous manifestations related to secondary syphilis are well-recognized, nodular vasculitis is extremely rare. The histopathology of nodular vasculitis is an affliction of the hypodermic vessels and of migratory thrombophlebitis, which ignores subjacent venous alterations.⁴⁶ These lesions should be distinguished from erythema nodosum, polyarteritis nodosa, tuberculosis, and a deep fungal infection. Jo et al.⁴⁷ reported an interesting case of secondary syphilis with uncommon clinical features resembling Behçet's disease and histopathological features of nodular vasculitis.

CONCLUSIONS

The occurrence of symptomatic syphilis including secondary syphilis is increasing in Korea. Considering the systemic effect of syphilis on individuals and public health, earlier detection of symptomatic syphilis must be established. We have widened the view of symptomatic secondary syphilis in this review.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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