

Case Report

Not peer-reviewed version

When Syphilis Imitates Cancer: A Case of Misdiagnosed Cutaneous T-Cell Lymphoma and Literature Review

[Ugo Giordano](#)^{*}, Jacek Kwiatkowski, [Krzysztof Zduniak](#), Monika Mordak-Domagala, Zuzanna Dybko, [Jarosław Dybko](#)

Posted Date: 10 October 2025

doi: 10.20944/preprints202510.0818.v1

Keywords: syphilis; differential diagnosis; malignancy; hematologic malignancy; lymphoma



Preprints.org is a free multidisciplinary platform providing preprint service that is dedicated to making early versions of research outputs permanently available and citable. Preprints posted at Preprints.org appear in Web of Science, Crossref, Google Scholar, Scilit, Europe PMC.

Copyright: This open access article is published under a Creative Commons CC BY 4.0 license, which permit the free download, distribution, and reuse, provided that the author and preprint are cited in any reuse.

Disclaimer/Publisher's Note: The statements, opinions, and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions, or products referred to in the content.

Case report

When Syphilis Imitates Cancer: A Case of Misdiagnosed Cutaneous T-Cell Lymphoma and Literature Review

Ugo Giordano ^{1,2}, Jacek Kwiatkowski ², Krzysztof Zduniak ², Monika Mordak-Domagala ², Zuzanna Dybko ³ and Jarosław Dybko ^{2,4}

¹ Department and Clinic of Endocrinology and Internal Medicine, Wrocław Clinical Hospital, 50-367 Wrocław, Poland

² Department of Hematology and Cellular Transplantation, Lower Silesian Oncology Center, 53-413 Wrocław, Poland

³ Faculty of Medicine, Wrocław Medical University, 50-367 Wrocław, Poland

⁴ Department of Oncology and Hematology, Faculty of Medicine, Wrocław University of Science and Technology, 50-370 Wrocław, Poland

* Correspondence: ugojiordano1@gmail.com

Abstract

Syphilis is a chronic infectious disease caused by *Treponema pallidum* which stands as one of the most significant imitators in clinical medicine. Its wide variety of manifestations can mimic autoimmune, inflammatory, and neoplastic disorders. Hereby we present a case of a 27-year-old male initially suspected of cutaneous T-cell lymphoma (CTCL) based on lymphadenopathy, systemic weight loss, ulcerative cutaneous lesions, and fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET-CT) findings of hypermetabolic nodes above and below the diaphragm. Histopathological analysis suggested pleomorphic lymphoid proliferation, while imaging supported the suspicion of malignancy. However, subsequent biopsies revealed plasmacytic and lymphocytic infiltration without clonality, and treponemal serologies confirmed secondary syphilis. The patient was referred for anti-treponemal therapy resulting in the resolution of the initial symptoms. This case highlights how syphilis can closely imitate hematologic malignancy, particularly CTCL, at both clinical and histopathological levels. We also review published reports of syphilis masquerading as malignancies and propose a structured diagnostic algorithm. We believe that the early inclusion of syphilis in differential diagnosis is critical to avoid misdiagnosis and appropriate treatment delays.

Keywords: syphilis; differential diagnosis; malignancy; hematologic malignancy; lymphoma

1. Introduction

Syphilis, caused by *Treponema pallidum*, has long been known as “the great imitator,” owing to its complex presentations across dermatologic, neurologic, cardiovascular, and hematologic systems [1]. In its secondary stage, syphilis frequently manifests with mucocutaneous lesions and generalized lymphadenopathy, but in atypical cases, its features overlap with malignant or autoimmune diseases [2,3]. This diagnostic challenge is compounded by the nonspecificity of modern imaging, such as FDG-PET-CT, which may show hypermetabolic lymph nodes in both malignant lymphoma and reactive infections [4,5].

Unusual presentations of syphilis have been reported, including pulmonary nodules, gastric masses, cervical ulcerations, skin rash, and widespread lymphadenopathy, often leading to an initial misdiagnosis of lymphoma or carcinoma [5–11], as presented in Table 1. Malignant syphilis, particularly in immunocompromised individuals such as those with HIV, may histologically and clinically resemble cutaneous T-cell lymphomas (CTCL) [7].

Given its rising incidence globally, especially among at-risk populations, syphilis should remain an essential part of differential diagnoses when assessing patients with systemic symptoms, lymphadenopathy, and cutaneous lesions suspicious for malignancy [2,12]. Herein, we present a patient initially suspected of CTCL, ultimately diagnosed with secondary syphilis, provide a review of similar cases from the literature, and propose a diagnostic algorithm.

Table 1. Reported cases of syphilis misdiagnosed as hematologic or non-hematologic malignancies.
Abbreviations: FDG-PET-CT - fluorodeoxyglucose positron emission tomography-computed tomography; CTCL - cutaneous T-cell lymphoma; HIV - human immunodeficiency virus; FNAC - fine needle aspiration cytology; CE-CT - contrast-enhanced computed tomography; RPR - rapid plasma reagin test; TPHA - treponema pallidum hemagglutination assay.

First author (Year)	Clinical presentation	Initial suspected diagnosis	Diagnostic pitfall	Final clue leading to syphilis diagnosis
Ohta et al. (2018) [4]	Chest pain, rash, stomatitis, generalized lymphadenopathy, pulmonary nodules	Metastatic lung cancer / lymphoma	FDG-PET-CT uptake in mediastinal/axillary nodes and lung nodules, nonspecific lymph node biopsy	Positive RPR/TPHA serology, resolution with antibiotics, contracted lung nodular shadows following treatment
Cerchione et al. (2017) [6]	Generalized lymphadenopathy, fever, weight loss, rash, hepatomegaly, splenomegaly, nocturnal sweating	Non-Hodgkin lymphoma	FDG-PET-CT hypermetabolic nodes, FNAC showing reactive hyperplasia, delayed rash misinterpreted as viral exanthema, negative flow cytometry assay for B/T cell clonality	Treponemal serology positive after repeated testing, regression with penicillin, high-risk sexual intercourse
Yamashita et al. (2015) [7]	HIV positivity, ulcerated skin lesions, fever, headache, and myalgia without lymphadenopathy	CTCL	Histology resembling CTCL with only CD8+ T-cell infiltrates	Negative TCR rearrangement, positive treponemal tests, detection of spirochetes

Lan et al. (2021) [5]	Epigastric pain, weight loss, endoscopic gastric mass	Gastric adenocarcinoma or lymphoma	Endoscopy and biopsy showing antral gastric ulcer with gastric retention, CE-CT and FDG-PET-CT suggesting gastric cancer	Immunohistochemistry for Treponema pallidum, positive serology, promiscuous partner, histopathology negative for cancer cells
Salah et al. (2024) – Case 1 [9]	Generalized erythematous plaques	Primary cutaneous marginal zone lymphoma	Skin biopsy - lymphocytic infiltrate with CD3+T-cells and CD20+ B-cells, B-cells positive for BCL2 and BCL6. Predominance of kappa positive plasma cells	Positive syphilis serology, immunohistochemical study showing spirochetes, negative flow cytometry
Salah et al. (2024) – Case 2 [9]	Severe gastritis and esophageal candidiasis followed by disseminated eruption	Drug eruption after antifungal therapy	Biopsy -lymphocytic infiltrate with atypical CD3+, CD8+, TCRbetaF1+ CD7 + T-cells, immunoreactivity for TIA-1 and granzyme B	Unremarkable bone marrow biopsy and flow cytometry, immunohistochemical study showing spirochetes, positive syphilis serology
Hodak et al. (1987) [11]	Cutaneous eruption with plasma cell infiltrate	Cutaneous lymphoma	Histology suggested lymphoma; histological reactive pattern	Serologic tests positive for syphilis, dark-field microscopy demonstrating spirochetes in a nodular lesion, clinical resolution after penicillin
Komeno et al. (2018) [10]	Bilateral cervical lymphadenopathy, pulmonary nodule, periportal lymph node	Malignant lymphoma	Histology of lymph nodes with adipose tissue with fibrosis, infiltration by lymphocytes with mildly expanded nuclei	Treponemal serology positive, clinical resolution after penicillin, history of oral sex with partners

Maci et al. (2025) [8]	HIV positivity under antiretroviral therapy, five-day history of fever and multiple lymphadenopathies, lung consolidation	Hematologic malignancy	Lymph node biopsy revealing disrupted architecture with multiple granulomas		Serological tests, clinical resolution after penicillin, regression of the lung consolidation by FDG-PET-CT
			multinucleated giant cells, negative anti-treponema immunoreaction		

2. Case Report

A 27-year-old male suffering from ankylosing spondylitis (HLA-B27 positive) was suspected of being affected by CTCL. The initial manifestation in June 2022 included progressive right cervical lymphadenopathy with a non-healing ulceration of the overlying skin. Also, the patient experienced an unintentional weight loss of 8 kg within 1.5 months (from 80 kg to 72 kg) without night sweats or fever. Laboratory tests revealed a mild, new-onset anemia (drop of hemoglobin concentration from 16 g/dL to 12.8 g/dL (N: 14-18 g/dL) in the observation period). In September 2022, an excisional biopsy of head and neck lesions and involved skin revealed an infiltration of pleomorphic CTCL (CD3 +++,CD20 +, Ki67 + in 10% of cells, Melan A -, HMB-45 +/-, MITF -, SOX10 -). At that time, a FDG-PET-CT scan showed active proliferative disease involving lymph nodes above and below the diaphragm with cutaneous involvement. Additional tests were carried out in October 2022, including:

- Biopsy of the ulcerated skin - abundant infiltration of plasmocytes and lymphocytes in the dermis proper without neoplastic lesions (Fig. 1A-D);
- Bone marrow biopsy - medium-density marrow, without the presence of abnormal cells, with changes in granulocytes and platelets consistent with vitamin B12 deficiency;
- Bone marrow cells flow cytometry - no evidence of abnormal clonal T-lymphocytes;
- Cytogenetics - no detectable TCRβ or TCRαδ gene rearrangements;
- Trephine biopsy - no presence of lymphoproliferative disease, consistent with reactive or inflammatory changes;
- Testing for infectious or autoimmune diseases (negative for HBV, HCV, HIV, HSV 1/2, VZV, HTLV I/II, EBV, CMV, antinuclear, intrinsic factor and gastric parietal cell antibodies).

With these results, in March 2023, the patient was admitted to our ward in order to continue the diagnostic workup. He was in good general condition, with persistent left cervical and bilateral inguinal lymphadenopathy (lymph nodes up to 1.5 cm and 1 cm, respectively). Cutaneous involvement was present as infiltrative skin lesions including the scar after lymph node biopsy on the neck, chest, trunk, back, and scrotum, without pruritus or scaling (Figure 1E, 1F). Further testing revealed an IgG4 level within normal ranges with, however, a positive result of the Waaler-Rose, fluorescent treponemal antibody absorption (antibody titre 1/4000), treponema pallidum hemagglutination assay (antibody titre 1/10240), and venereal disease research laboratory (antibody titre 1/128) tests. Considering the positive treponema pallidum tests, and results of trephine and ulcerated skin biopsy (Figure 1A-D) suggesting the occurrence of an inflammatory process, a suspected syphilis diagnosis with skin involvement was made. The higher lymph node metabolic activity both above and below the diaphragm in the PET-CT scan from October 2022 was deemed secondary to the ongoing inflammatory process. As a consequence, in April 2023, the patient was referred to the Infectious Disease Department for treatment continuation.

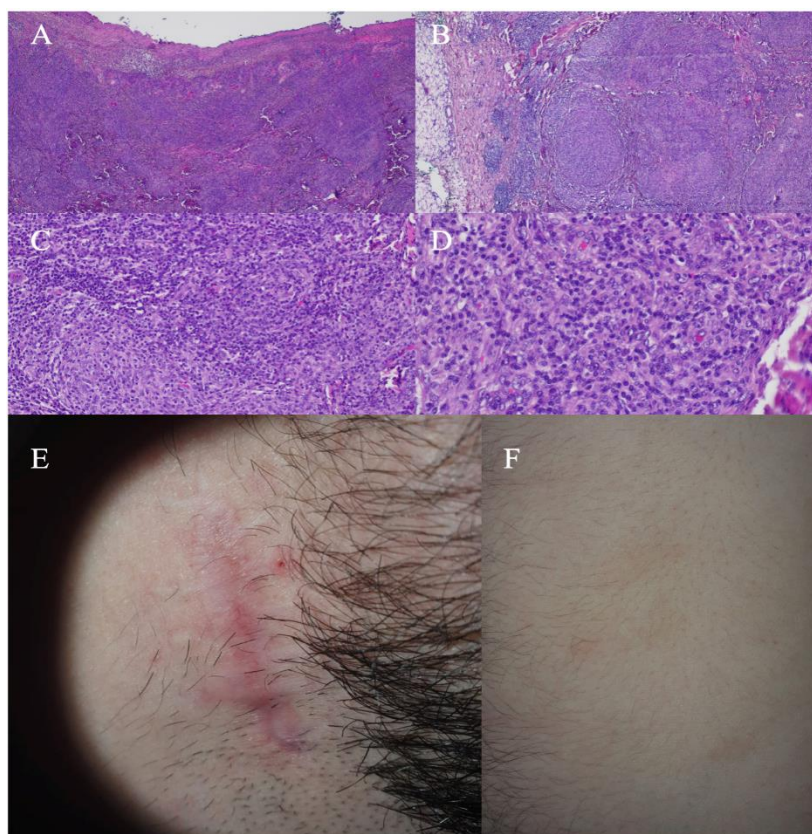


Figure 1. Histopathological examination of the ulcerated skin from October 2022 (A-D; HE x20, x40, x200, x400, respectively). Histologically skin lesions presented as ulcerated tumors, composed mostly of ill-defined non-necrotizing granulomas and numerous mature plasma cells, which were polytypic on kappa/lambda immunohistochemistry. Mature lymphocytes, predominantly T-cells, were relatively sparse. There were some dispersed immunoblasts. Diagnosis of reactive, inflammatory lesions was rendered with suggestion of infectious disease. Ulceration in the right submandibular space in the scar after biopsy (E). Disseminated lesions on the skin of the chest and abdomen (F).

4. Case Report

Syphilis continues to present significant diagnostic challenges due to its ability to mimic both hematologic and solid malignancies. In our case, the initial constellation of cervical lymphadenopathy, systemic weight loss, ulcerative cutaneous lesions, and FDG-PET-CT findings raised a strong suspicion of CTCL. Histopathology revealed pleomorphic lymphoid infiltration, while FDG-PET-CT demonstrated widespread hypermetabolic lymph nodes, further supporting this suspicion. However, repeated biopsies showed reactive plasmacytic infiltration without clonality, and subsequent treponemal serologies confirmed secondary syphilis. This illustrates the remarkable ability of syphilis to imitate lymphoma at multiple diagnostic levels [6,13].

The histopathological features of syphilitic lymphadenitis - including follicular hyperplasia, non-necrotizing granulomas, and polytypic plasma-cell infiltrates - may closely resemble those seen in lymphoma or IgG4-related disease [5,12,14]. Immunophenotyping often reveals a mixture of T- and B-lymphocytes without clear clonality, which can be interpreted as an early lymphoproliferative disorder unless molecular studies exclude it [6]. Similarly, FDG-PET-CT imaging, while highly sensitive for malignant lymphoma, lacks specificity; syphilitic lymphadenitis can demonstrate marked FDG uptake indistinguishable from aggressive lymphoma [4,5,8]. Thus, reliance solely on histology or imaging may perpetuate misdiagnosis.

Several case reports highlight this dilemma, as demonstrated in Table 1. Ohta et al. described generalized lymphadenopathy with pulmonary lesions mimicking lymphoma, ultimately diagnosed as syphilis after treponemal serology [4]. Cerchione et al. reported a patient with FDG-PET-CT

hypermetabolic nodes initially misdiagnosed as lymphoma until a late syphilis diagnosis was established [6]. Yamashita et al. presented malignant syphilis in an HIV-positive patient, clinically and histologically resembling CTCL but lacking T-cell receptor clonality [7]. Other reports document gastric syphilis mimicking adenocarcinoma or lymphoma [5], skin manifestations initially diagnosed as drug eruption after antifungal therapy and primary cutaneous marginal zone lymphoma [9]. Cervical lymph node involvement with pulmonary nodules has also been misinterpreted as lymphoma [8,10].

Common diagnostic pitfalls across these cases include reliance on imaging suggestive of malignancy, nonspecific histology, and failure to consider syphilis serology early in the workup. Ultimately, serological testing, confirmatory immunohistochemistry or PCR for *T. pallidum*, and clinical resolution following penicillin therapy provide the final diagnostic confirmation. Our case adds to the already present scientific reports that polytypic plasma-cell infiltration without clonality and FDG-PET-CT findings of widespread hypermetabolism should always prompt consideration of syphilis, particularly in young patients or those with risk factors. Based on our expertise and on previous scientific reports, we propose a diagnostic algorithm that may be of use to clinicians in their daily clinical practice (Figure 2).

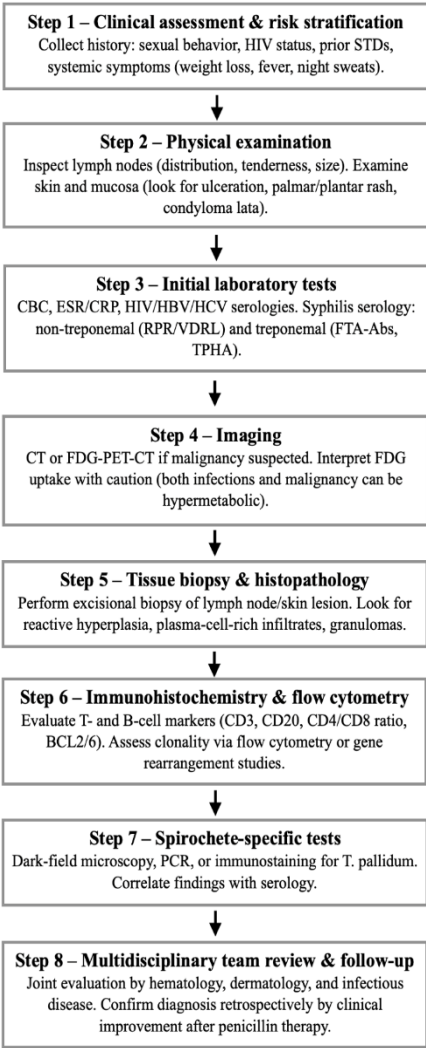


Figure 2. Proposed diagnostic workup of syphilis. Abbreviations: STD - sexually transmitted diseases; CBC complete blood count; ESR - erythrocyte sedimentation rate; CRP - C-reactive protein; HIV - human immunodeficiency virus; HBV - hepatitis B virus; HCV - hepatitis C virus; RPR - rapid plasma reagin test; VDRL - Venereal Disease Research Laboratory test; FTA-Abs - fluorescent treponemal antibody absorption; TPHA -

Treponema pallidum hemagglutination assay; CT - computed tomography, FDG-PET-CT fluorodeoxyglucose positron emission tomography combined with computed tomography; PCR - polymerase chain reaction.

5. Conclusions

This case and reviewed literature emphasize that syphilis remains an important imitator of hematologic and non-hematologic malignancies. When patients present with lymphadenopathy, systemic symptoms, and cutaneous lesions suspicious for lymphoma, syphilis should be included early in the differential diagnosis, especially in patients at risk. Serologic testing is widely available, hence its implementation may prevent invasive diagnostics and inadequate therapies. Histopathology showing reactive plasmacytic infiltration without clonality, or a positive FDG-PET-CT with tracer uptake not proportionate to clinical presentation, should especially incline towards considering syphilis. A multidisciplinary approach is essential to avoid delays in diagnosis and, eventually, reduce patient morbidity. Ultimately, systematic inclusion of syphilis in diagnostic workups can avert misdiagnosis and unnecessary treatment, underscoring its relevance as “the great imitator” in modern hematology and internal medicine [1,2,12].

Author Contributions: Conceptualization, U.G., J.D., J.K.; methodology, U.G., J.D., J.K.; investigation, U.G.; software, K.Z., Z.D.; data curation, U.G., Z.D.; writing— U.G; original draft preparation, U.G.; writing—review and editing, U.G., J.D.; supervision, J.D., M.M-D., J.K. All authors have read and agreed to the published version of the manuscript.

Funding: This manuscript received no external funding.

Institutional Review Board Statement: Ethical review and approval were waived for this study due to local regulations: case reports are not required to be approved by local ethical committee if they describe standard diagnostic and therapeutical procedures. Our cases were diagnosed and treated according to internationally and locally approved standards.

Informed Consent Statement: Informed consent was obtained from the patient involved in the study. Written informed consent has also been obtained from the subject to publish this paper.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

FDG-PET-CT	Fluorodeoxyglucose positron emission tomography–computed tomography
CTCL	Cutaneous T-cell lymphoma
HIV	Human immunodeficiency virus
FNAC	Fine needle aspiration cytology
CE-CT	Contrast-enhanced computed tomography
RPR	Rapid plasma reagin test
TPHA	Treponema pallidum hemagglutination assay
STD	Sexually transmitted diseases
CBC	Complete blood count
ESR	Erythrocyte sedimentation rate

CRP	C-reactive protein
HBV	Hepatitis B virus
HCV	Hepatitis C virus
VDRL	Venereal Disease Research Laboratory test
FTA-Abs	Fluorescent treponemal antibody absorption test
CT	Computed tomography
PCR	Polymerase chain reaction

References

1. Hook, E.W., 3rd; Marra, C.M. Acquired Syphilis in Adults. *N. Engl. J. Med.* 1992, 326, 1060–1069.
2. Ghanem, K.G.; Ram, S.; Rice, P.A. The Modern Epidemic of Syphilis. *N. Engl. J. Med.* 2020, 382, 845–854.
3. French, P. Syphilis. *BMJ* 2007, 334, 143–147.
4. Ohta, A.; Furusyo, N.; Kishihara, Y.; Eiraku, K.; Murata, M.; Kainuma, M.; Toyoda, K.; Ogawa, E.; Hayashi, T.; Koga, T. Secondary Syphilis with Pulmonary Involvement. *Intern. Med.* 2018, 57, 121–126.
5. Lan, Y.-M.; Yang, S.-W.; Dai, M.-G.; Ye, B.; He, F.-Y. Gastric Syphilis Mimicking Gastric Cancer: A Case Report. *World J. Clin. Cases* 2021, 9, 7798–7804.
6. Cerchione, C.; Maraolo, A.E.; Marano, L.; Pugliese, N.; Nappi, D.; Tosone, G.; Cimmino, I.; Cozzolino, I.; Martinelli, V.; Pane, F.; et al. Secondary Syphilis Mimicking Malignancy: A Case Report and Review of Literature. *J. Infect. Chemother.* 2017, 23, 576–578.
7. Yamashita, M.; Fujii, Y.; Ozaki, K.; Urano, Y.; Iwasa, M.; Nakamura, S.; Fujii, S.; Abe, M.; Sato, Y.; Yoshino, T. Human Immunodeficiency Virus-Positive Secondary Syphilis Mimicking Cutaneous T-Cell Lymphoma. *Diagn. Pathol.* 2015, 10, 185.
8. Maci, C.; Canetti, D.; Tassan Din, C.; Bruzzesi, E.; Lucente, M.F.; Badalucco Ciotta, F.; Candela, C.; Ponzoni, M.; Castagna, A.; Nozza, S. Malignant Syphilis Mimicking Lymphoma in HIV: A Challenging Case and a Review of Literature Focusing on the Role of HIV and Syphilis Coinfection. *Microorganisms* 2025, 13, 968.
9. Salah, H.; Prieto, V.; Cho, W.C.; Torres-Cabala, C.; Lenskaya, V. (virtual) the Misleading Syphilis: Two Cases Masquerading as Lymphomas. In *Proceedings of the ASDP 61st Annual Meeting; ASDP Proceedings*, November 4 2024.
10. Komeno, Y.; Ota, Y.; Koibuchi, T.; Imai, Y.; Iihara, K.; Ryu, T. Secondary Syphilis with Tonsillar and Cervical Lymphadenopathy and a Pulmonary Lesion Mimicking Malignant Lymphoma. *Am. J. Case Rep.* 2018, 19, 238–243.
11. Hodak, E.; David, M.; Rothem, A.; Bialowance, M.; Sandbank, M. Nodular Secondary Syphilis Mimicking Cutaneous Lymphoreticular Process. *J. Am. Acad. Dermatol.* 1987, 17, 914–917.
12. Singh, A.E.; Romanowski, B. Syphilis: Review with Emphasis on Clinical, Epidemiologic, and Some Biologic Features. *Clin. Microbiol. Rev.* 1999, 12, 187–209.
13. Ohta, M. Secondary Syphilis with Generalized Lymphadenopathy and Pulmonary Involvement Mimicking Lymphoma. *Intern Med* 2019, 58, 1813–1816.
14. Bledsoe, J.R.; Della-Torre, E.; Rovati, L.; Deshpande, V. IgG4-Related Disease: Review of the Histopathologic Features, Differential Diagnosis, and Therapeutic Approach. *APMIS* 2018, 126, 459–476.

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.