Secondary Syphilis Unmasked by BNT162b2 mRNA COVID-19 Vaccine

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Pre-antibiotic studies have indicated that two-thirds of patients with syphilis will clear the infection spontaneously [1]. The median incubation period of primary syphilis is 21 days (range 3–90 days), while secondary syphilis begins 4–10 weeks after the occurrence of a chancre. The coronavirus disease 2019 (COVID-19) epidemic, which began in late-2019 and reached Israel in February 2020, has put a tremendous strain on access to regular medical care. In late December 2020, Israel was one of the first countries to rapidly deploy the Comirnaty (BNT162b2, BioNTech/Pfizer) vaccine [2]. This vaccine has shown some rare and unusual adverse effects, such as reactivation of herpes zoster [3]. In April 2021 we cared for a patient who developed symptoms of secondary syphilis more than a year after his last sexual contact. His symptoms had commenced 2 weeks after the second dose of the Comirnaty vaccine, but he was diagnosed only a month later by an attentive physician.

PATIENT DESCRIPTION

A homosexual man in his 40s received his first Comirnaty vaccine on 26 January 2021 and the second dose on 16 February 2021. Two weeks after the second dose he started developing a maculopapular rash on his chest, back, and legs. The rash on his legs was painful, and he felt a burning sensation when walking. In addition, he was myalgic and complained of headaches, but no fever. He was seen by his primary care physician on 7 March 2021. His physician noted a pink-scaly rash for which he was sent to see a dermatologist and to complete some blood tests [Table 1].

The initial tests revealed a drop in his hemoglobin level from an average of 14 to 12 g/dl, and a low iron saturation, which was ascribed to his low-meat diet. He was seen by a dermatologist on 4 April 2021. The dermatologist noted a psoriasiform rash for which he was sent to do a biopsy. However, that night he developed a fever of 39°C, and he self-referred to a local hospital. Blood tests at the emergency department were remarkable for hemoglobin of 10.8, a C-reactive protein (CRP) of 13.8 (n < 0.5), and gamma-glutamyl transferase of 90.

Chest X-ray was suspicious for a lobar pneumonia, for which he was prescribed levofloxacin 750 mg/day. He was sent home, but not before an attentive physician requested serology for human immunodeficiency virus and syphilis. Those test results came back 4 days later: the HIV was negative, while treponema pallidum hemagglutination was positive and the rapid plasma regain (RPR) test showed a titer of 1:256.

On 14 April 2021 he was seen by an infectious diseases consultant. On questioning, the patient adamantly denied having any relationship (sexual or other) during the COVID-19 epidemic period (at least one year). He was prescribed three intramuscular shots of benzathine-penicillin 2.4 mill/week for 3 weeks. Three days later he felt improvement in his myalgic pain, although the rash on his legs remained for more than a month. Two months after his first visit the CRP had dropped to 1.2 and the RPR to 1:64.

COMMENT

This case highlights two unique points: the capability of primary syphilitic infection to go undetected for a year and the possible reactivation of this infection to the Comirnaty COVID-19 vaccine.

Syphilis has often been referred to as the great masquerader, as it may present with a wide array of clinical symptoms and signs [4]. An accurate history taking coupled with the realization of the recent upsurge of cases of syphilis among men who have sex with men (MSM) could have yielded a quicker diagnosis. Worldwide, syphilis infected 11.8% of MSM in 2019 [5]. In the United States alone, the number of cases of primary and secondary syphilis increased in 2018 to 35,000, the highest number since 1991. Syphilis has been named by some, the stealth pathogen, due to its ability to evade the immune system. Secondary syphilis with its protean manifestations usually appears 4–10 weeks after the primary chancre, but in a non-negligible proportion of patients they will move into latency unnoticed. Approximately 25% of these patients will experience one or more bouts of secondary-like syphilis during early latency [4], as occurred in our patient.

Table 1: Blood tests

	Date		
Test	**15 March 2021**	**5 April 2021**	**20 May 2021**
Hemoglobin (g/dl)	11.9	11.5	13.2
Hematocrit	38.9	36.2	42.1
Iron (normal 70–180)	52	14	
Transferrin	303	221	
White Blood Cell count	5000	9200	6700
Alkaline phosphatase (normal 30–120)	253	128	65
Gamma glutamyl transferase (normal < 55)		90	21
Gamma glutamyl transferase (normal < 37)	74	19	16
Aspartate transaminase (normal < 37)	44	16	
C-reactive protein (normal < 0.5)		13.5	1.2
Erythrocyte sedimentation rate		60/hour	
Human immunodeficiency virus		Negative	
Treponema pallidum hemagglutination		Positive	Positive
Rapid plasma regain test		1:256	1:64

The immunity of syphilis is complex. It may be regarded as contest between the ability of *Treponema pallidum* to avoid recognition and the skill of the innate and adaptive immune system to mark and kill the invader. *T. pallidum* lacks lipopolysaccharide, which is a major proinflammatory glycolipid in its outer-membrane-protein. In addition, spirochetes are not easily cleared by opsonic antibody. In other words, they are resistant to antibody binding. Altogether, this allows the bacterium to undergo repeated bouts of dissemination that are poorly detected by innate immunity, and explain the lack of systemic inflammatory symptoms characteristic of the second stage of the disease. The pathogenesis of classical syphilis involves recognition of the lipopeptides of *T. pallidum* through the TLR-2 pathway by dendritic cells (DC). These DCs act as a bridge between the innate and adaptive immune systems and present the antigens to T-cells together with production of inflammatory cytokines such as interleukin-1β, IL-6, IL-12, and tumor necrosis factor (TNF-α).

The pathogenesis of COVID-19 involves two stages: the viral replication stage (days 1–10) and the immune dysfunction stage (days 8–14). During the cytokine storm of the second stage, inflammatory cytokines such as IL-1, IL-6, GM-CSF, INF-gamma, and TNF interact with the complement and coagulation systems to induce disseminated intravascular coagulation, respiratory failure and more. A milder immune activation also occurs with the new mRNA vaccines approved for use in Israel (e.g., Pfizer's BNT162b2 vaccine). The mRNA nanoparticles gain entry into dendritic cells, resulting in production of high levels of S protein. In addition, innate sensors (such as TLR-7) are triggered by the intrinsic adjuvant activity of the vaccine to produce type I interferon and multiple pro-inflammatory cytokines and chemokines. In parallel, the activated dendritic cells present the antigen to naïve T-cells, which become activated and differentiate into effector T-cells and memory T-cells. The T-follicular helper cells help S protein-specific B-cells to differentiate into antibody-secreting plasma cells.

The sequence of events in this case led the physicians to speculate that the milder cytokine activation that occurred following the second Pfizer BNT162b2 vaccine acted like an adjuvant of the spirochetes. Once these stealth organisms were recognized by the immune system, a florid second stage syphilis ensued. However, which cytokines was the specific trigger is unclear. We also believe that these events may help in the search for a syphilis vaccine. Interestingly, a few reports have described reactivation of herpes zoster following the BNT162b2 vaccine [3] or flare-ups of immune-mediated diseases.

CONCLUSIONS

It is important to recognize that some cases of secondary syphilis may present a year or more after infection and that the newer COVID-19 vaccines may act as an adjuvant to enable recognition of this stealth pathogen by the immune system.

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