LYMPHOPENIA AND TUBERCULOUS LYMPHADENITIS UNDER IMMUNOMODULATORY AGENTS IN A MULTIPLE SCLEROSIS PATIENT: FOLLOW-UP OF A CHALLENGING CASE

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Interferon-beta (IFN-β) 1a and glatiramer acetate (GA) are first-line therapies for multiple sclerosis (MS) with immunomodulatory effects. We present a patient who developed lymphopenia and tuberculous lymphadenitis under treatment with these agents.

The female patient who at present 65 year old is followed at our MS outpatient clinics had received GA (20 mg/day, subcutaneous injection) and later IFN-β 1a (44 μg, thrice weekly, subcutaneous injection). During the course of her treatment, she developed mild to severe lymphopenia.

A follow up thoracic spinal MRI (when lymphocyte count was 800/μl) showed multiple enlarged lymph nodes in the posterior mediastinum incidentally. Further investigation revealed tuberculous lymphadenitis. She received anti-tuberculosis (TB) treatment for nine months and her condition resolved.

Although immunomodulatory treatments are considered safe with regard to opportunistic infections, and lymphopenia under these treatments are generally accepted as mild and asymptomatic, our experience was different with this patient. Further studies on the management of patients with lymphopenia and assessment of the risk of TB under immunomodulatory agents are needed.

Keywords: *tuberculous lymphadenitis, interferon beta 1a, interferon adverse events, multiple sclerosis*

ESETBEMUTATÁS: SCLEROSIS MULTIPLEXBEN SZENVEDŐ BETEGBEN IMMUNMODULÁNS KEZELÉS SORÁN KIALAKULT LYMPHOPENIA ÉS TUBERCULOSUS LYMPHADENITIS

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Az interferon-β- (IFN-β) 1a és a glatiramer-acetát (GA) a sclerosis multiplex (SM) első vonalbeli kezelésében használatos immunmoduláns szerek. Egy olyan SM-beteg esetét mutatjuk be, akinél ezen immunmoduláns szerek alkalmazása során lymphopenia és tuberculous lymphadenitis alakult ki.

Az SM-ambulanciánkon kezelt, jelenleg 65 éves nőbeteg korábban 20 mg/nap subcutan GA-, majd heti háromszor 44 μg subcutan IFN-β 1a-terápiában részesült.

Immunmoduláns kezelése során enyhe-súlyos lymphopenia alakult ki nála. Utánkövetése során (800/μl lymphocytaszámnál) thoracalis gerinc-MR-felvételén a posterior mediastinumban számos megnagyobbodott nyirokcsomó ábrázolódott. A további vizsgálat tuberculosus lymphadenitist igazolt. Ezt követően kilenc hónapig tuberculosis (tbc) elleni kezelésben részesült, és tbc-fertőzése megszűnt.

Habár az immunmoduláns kezelést az opportunisztikus fertőzések kialakulása szempontjából biztonságosnak tartják, és az immunmoduláns kezelés során kialakuló lymphopenia általában enyhe és tünetmentes, a bemutatott esetben nem ez történt. További vizsgálatokra van szükség annak kiderítése érdekében, hogyan kell a lymphopeniás betegeket kezelni, és milyen mértékű a tbc kialakulásának kockázata immunmoduláns kezelés során.

Kulcsszavak: *tuberculosus lymphadenitis, interferon-β-1a, interferon-mellékhatások, sclerosis multiplex*

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Interferon-beta (IFN-β) 1a and glatiramer acetate (GA) are disease-modifying therapies (DMT) used in relapsing-remitting multiple sclerosis (RRMS)[1]. They are generally considered safe regarding opportunistic infections[1, 2]. Here, we report a patient with lymphopenia under treatment with GA and later with IFN-β 1a who developed tuberculous lymphadenitis.

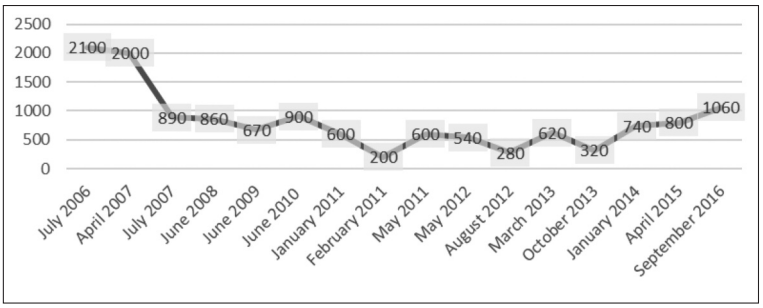

Figure 1. *Number of lymphocytes (/μl) over the years*

Case report

A 51 year old female presented with imbalance and speaking difficulty in July 2006 and applied to a tertiary center. She did not have any other disease and was not under any medication. Family history did not feature any demyelinating or connective tissue disease. Neurological examination showed dysarthria, increased deep tendon reflexes and mild ataxia (Extended Disability Status Scale/EDSS: 2.5). Physical examination (other than central nervous system) and extended laboratory tests were unremarkable from the point of vasculitis and connective tissue diseases. No significant feature was found on chest radiography.

Magnetic resonance imaging (MRI) of her brain showed multiple T2 hyperintense white matter lesions perpendicular to the lateral ventricles and also at the brainstem level, some of which had contrast enhancement.

She was diagnosed with RRMS according to 2005 Revised McDonald Criteria and received corticosteroids (1 gr/day methylprednisolone) for 6 days.

She applied to our outpatient clinic in October 2006. She refused immunomodulatory treatment at that point, however she had an attack with worsening of imbalance in March 2007. She received 5 days of corticosteroids and gave her consent to start glatiramer acetate (20 mg/day, subcutaneously/s.c.). She was clinically stable but her lymphocyte count decreased to 860 /μl in July 2007. Her therapy was continued and lymphocyte count persisted between 600-900 /μl from 2007 to 2011. In the meantime she had two clinical attacks (2008, 2010) and received 7 days of corticosteroids each time with an end EDSS of 3.5.

Immunosuppressive treatment options were considered with close follow up, however the patient had a relative who suffered from serious side effects of immunosuppressants, and she refused to receive any of them. She was finally switched to IFN-β 1a (44 μg, thrice weekly, s.c.) in January 2011. A month later, her lymphocyte count dropped to 200 /μl, the treatment was stopped and restarted 3 months later, when lymphocyte level was 600 /μl. Between 2011-2015 her therapy had to be paused two more times due to severe lymphopenia (below 400 /μl). **Figure 1** shows peripheral blood lymphocyte counts at some of her visits over the years.

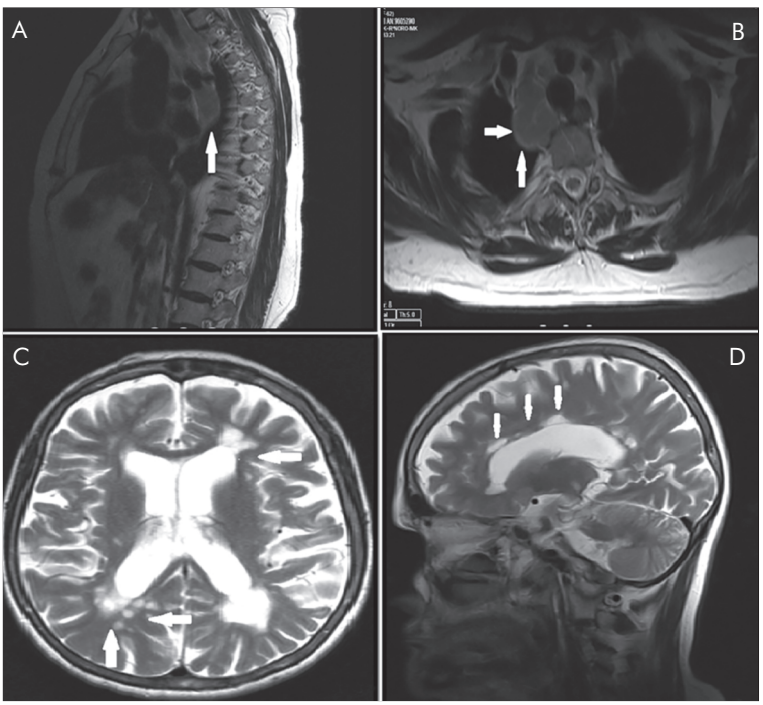

Figure 2. **A.** *Sagittal and* **B**. *axial sections of thoracic spinal MRI showing enlarged lymph nodes (the largest one being 19 × 21 mm - white arrows).* **C**. *Horizontal and* **D.** *sagittal sections of cranial MRI of the same patient demonstrating T2 hyperintense periventricular lesions (white arrows) compatible with multiple sclerosis*

In May 2015, she had undergone a follow up thoracic spinal MRI and multiple enlarged lymph nodes (LN) were detected in the posterior mediastinum incidentally. Previous thoracic MRIs (in 2007 and 2010) were normal regarding paravertebral and posterior mediastinum structures. **Figure 2** shows sections of cranial and thoracic spinal MRI in 2015.

She was referred to a tertiary center specialized on pulmonary diseases. Thorax Computerized Tomography showed multiple lymphadenopathies (LAPs), most prominently on left supraclavicular and right para-tracheal areas (**Figure 3.A, B**). Fine needle aspiration biopsy of supraclavicular LN was inconclusive. Excisional biopsy showed necrotizing granulomatous lymphadenopathy consistent with tuberculous lymphadenitis. IFN-β 1a treatment was discontinued. She is a housewife with medium socioeconomic status. She had no known contact with an active TB patient and received TB vaccination (Bacillus Calmette– Guérin, BCG) as a child. She had no history of consuming non-pasteurized milk. She was also on paroxetine 20 mg/day and piracetam 2400 mg/day since 2012. She had been treated with quadruple anti-tuberculosis treatment for nine months, then her condition resolved. She refused to receive any specific treatment for MS from this point on. Her condition has been consistent with secondary progressive phase within the last 3 years (Last EDSS: 5.5).

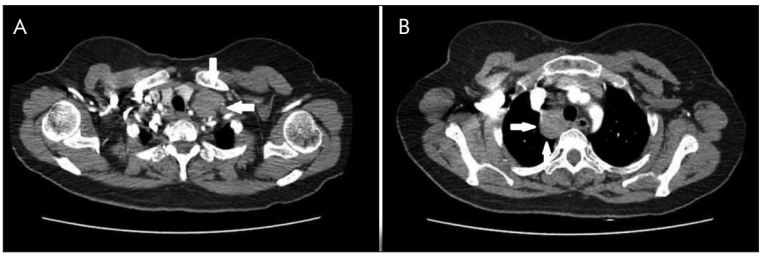

Figure 3. *Thorax CT showing* **A.** *3 × 4 cm mass lesion starting from left supraclavicular area and descending towards anterior mediastinum (white arrow)* **B.** *4.2 × 3 cm mass lesion on the right paratracheal area (white arrows) and multiple smaller mass lesions suggesting lymphadenopathies*

Discussion

IFN-β 1a and GA alter the secretion of different cytokines and immune cell functions to suppress inflammatory response. Therefore, they might be expected also to facilitate infections. IFN-β 1a can cause abscess formation at injection site and GA can lead to respiratory tract infections, cystitis and vaginitis, etc. However, they are generally considered safe regarding opportunistic infections[1, 2].

GA can rarely cause leukocytosis or mild leukopenia. IFN-β1a can cause mild, asymptomatic dose-related reductions in WBC lines that resolve within 3-4 months, even when the treatment is continued[3].

The mechanisms of action of IFN-β1a is complex and not entirely understood. It's been used in MS treatment due to increased expression of some anti-inflammatory cytokines and inhibition of pro-inflammatory pathways by IFN-β1a. In fact, IFNs are now known to change expressions of over 500 genes in the human body[4]. These diverse effects may possess unexpected and undesired consequences even in the absence of overt lymphopenia.

There are three types of interferons in the body, which are type I, II and type III. Type-I includes IFN-β1a and 1b and type II involves IFNγ. Recent studies showed that, while IFNγ plays important role against mycobacterial infections, type-I IFNs have anti-protective effects through increased apoptosis, inhibition of Thelper-1 and IFNγ responses[5]. They also increase IL-10 secretion which shifts balance toward anti-inflammatory Thelper-2 production and decrease T cell migration[4, 5]. There are also in vitro studies demonstrating that IFN-α/β treatment can disrupt immune defense against mycobacterial infections[6, 7].

We have found only one case report of TB in MS patients under interferon beta treatment. *Sirbu* et al.[8] recently reported four patients with active pulmonary TB under IFN β-1b therapy. The patients were diagnosed with TB after 12-84 months of treatment and received anti-TB therapy for 6-12 months. Interferon was discontinued in the meantime. Total WBC or lymphocyte counts were not included in the article.

There is no proven correlation between lymphopenia and drug efficiency; however, lymphopenia may carry additional risks of infection[3]. There are no exact guidelines regarding the management of patients with lymphopenia under DMTs.

Corticosteroids can also impair immunity against opportunistic infections[2]. Our patient received corticosteroids multiple times; however, they were at long intervals from each other and the last dose was approximately 4 years before TB. These were unlikely to affect the immune system at the time of TB diagnosis.

Our patient had previous chest X-Ray and thoracic MRIs that did not suggest TB. She did not

possess any known risk factors or develop any signs of TB before. She had normal lymphocyte counts and was vaccinated. So, it was very unlikely that she had active TB previously. However, specific tests for TB were not performed before DMTs and this can be interpreted as a limitation for this case.

Current expert opinion does not recommend initial screening for latent TB unless there are other risk factors[9]. Genes that create tendency to TB can also give insight for susceptible individuals in the future[10].

To our knowledge, this is the first documented case of TB under IFN-β 1a treatment. Our patient had persisting mild to severe lymphopenia under GA and later under IFN-β 1a, and was diagnosed with TB lymphadenitis. We believe that lymphopenia started when she received GA and became more prominent, and symptomatic with IFN-β 1a. IFN-β 1a actions that are associated with impaired host defense against mycobacterial infections may have contributed to this process. There is no definitive data about artificial IFN-β preparations' effects regarding mycobacterial infections in MS patients; however, recent data raise reasonable questions.

Conclusion

Although there are years of experience with some of our current MS treatments, there are still some aspects that deserve further attention. Selection of patients for TB screening before or during DMTs and correct approach to lymphopenia under DMTs are vital problems that need further studies.

CONFLICT OF INTEREST
All authors declare no conflict of interest.

REFERENCES

1. *Winkelmann A, Loebermann M, Reisinger EC, Zettl UK*. Multiple sclerosis treatment and infectious issues: update 2013. Clin Exp Immunol 2014;175:425-38. https://doi.org/10.1111/cei.12226
2. *Epstein DJ, Dunn J, Deresinski S.* Infectious complications of multiple sclerosis therapies: ımplications for screening, prophylaxis, and management. Open Forum Infect Dis 2018;5:ofy174. https://doi.org/10.1093/ofid/ofy174
3. *Fox EJ, Buckle GJ, Singer B, Singh V, Boster A*. Lymphopenia and DMTs for relapsing forms of MS: Considerations for the treating neurologist [published correction appears in Neurol Clin Pract 2019;9(3):184]. Neurol Clin Pract 2019;9:53-63. https://doi.org/10.1212/CPJ.0000000000000567
4. *Jakimovski D, Kolb C, Ramanathan M, Zivadinov R, Weinstock-Guttman B*. Interferon béta for multiple sclerosis. Cold Spring Harb Perspect Med 2018;8(11):a032003. https://doi.org/10.1101/cshperspect.a032003
5. *Travar M, Petkovic M, Verhaz A*. Type I, II, and III Interferons: Regulating Immunity to Mycobacterium tuberculosis ınfection. Arch Immunol Ther Exp (Warsz) 2016;64(1): 19-31. https://doi.org/10.1007/s00005-015-0365-7
6. *Manca C, Tsenova L, Bergtold A, Freeman S, et al.* Virulence of a Mycobacterium tuberculosis clinical isolate in mice is determined by failure to induce Th1 type immunity and is associated with induction of IFN-alpha/beta. Proc Natl Acad Sci 2001;98:5752-7. https://doi.org/10.1073/pnas.091096998
7. *Bouchonnet F, Boechat N, Bonay M, et al*. Alpha/beta interferon impairs the ability of human macrophages to control growth of *Mycobacterium bovis* BCG. Infect Immun 2002;70:3020-5. https://doi.org/10.1128/IAI.70.6.3020-3025.2002
8. *Sirbu CA, Dantes E, Plesa CF, et al.* Active pulmonary tuberculosis triggered by ınterferon beta-1b therapy of multiple sclerosis: Four case reports and a literature review. Medicina 2020;56:202. https://doi.org/10.3390/medicina56040202
9. *Navas C, Torres-Duque CA, Munoz-Ceron J, et al*. Diagnosis and treatment of latent tuberculosis in patients with multiple sclerosis, expert consensus. On behalf of the Colombian Association of Neurology, Committee of Multiple Sclerosis. Mult Scler J Exp Transl Clin 2018;4(1): 2055217317752202. https://doi.org/10.1177/2055217317752202
10. *Möller M, Kinnear CJ , Orlova M, Kroon EE, et al*. Genetic resistance to mycobacterium tuberculosis ınfection and disease. Front Immunol 27 September 2018. https://doi.org/10.3389/fimmu.2018.02219