Reply to “Jacobsen Syndrome in a Patient with Combined Immunodeficiency, Thrombocytopenia, and Lymphoma”

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To the Editor:

We thank Professor Özdemir for his interest in our case report “Immunodeficiency and lymphoma in Jacobsen syndrome” [1].

We are aware that Jacobsen syndrome (JS) is now recognized as an inborn error of immunity (IEI), specifically primary immunodeficiency, as we discussed in our case report [2]. JS has also been recently described elsewhere [3]. According to the classification of the International Union of Immunological Societies, JS is classified in the table of combined immunodeficiencies with associated or syndromic features [4]. To our knowledge, we reported the first case of a patient with JS and lymphoma. Immunoglobulin replacement therapy (IRT) was administered from the age of 8 years until the age of 12. However, records from that time are missing, and despite active research, no documents could be found. The patient had no specialized follow-up. Thereafter, no relevant infections were observed until the age of 46 years, when, after chemotherapy, multiple ENT and lung infections (3-5 episodes per year) required outpatient antibiotic treatment. During this period, the patient was not admitted to hospital with infections and underwent no specialized follow-up. Unfortunately, as we also stated in our case report, information on immunoglobulin levels prior to chemotherapy and detailed records of infections and antibiotic treatment were unavailable. IRT 0.4 g/kg/mo is ongoing. Finally, a genetic evaluation was requested owing to the syndromic nature and unusual clinical presentation. The diagnosis of JS was made after the third chemotherapy cycle. An immunological evaluation was not requested at the time, since the patient showed no initial signs of infection (ENT and lung) until after chemotherapy. The patient has combined immunodeficiency and permanent lung damage with bronchiectasis, as stated in our case report [2]. He continues to be followed up by the Departments of Immunology and Oncology 3 years after chemotherapy. We concur with the view that the patient will likely need lifelong IRT treatment.

IEI comprise a heterogeneous group of disorders. Several factors can influence the development of different cancer types [5]. It is therefore important that immunologists and oncologists work together to monitor and make an early diagnosis of the potential development of cancer in known cases of IEI, as well as underlying IEI in newly diagnosed cancers with a suggestive medical history or a high rate of therapy-related toxicity. We are aware that the risk of developing a malignancy is dramatically increased in IEI. We deemed it important to highlight that the 11q deletion in the case we reported is likely associated with JS, immunodeficiency, and lymphoid neoplasm. Deletion of ETS1, for example, may play a role in the malignant transformation of hematopoietic neoplasms, including B-cell malignancies [6].

Since genetic testing was not performed previously, it was requested owing to the syndromic nature of the conditions with lymphoma. The diagnosis of JS was made after the third chemotherapy cycle. The patient eventually received the standard dose and number of cycles (6) of R-EPOCH (rituximab 570 mg, etoposide phosphate 75 mg/m², prednisone 60 mg/m², vincristine sulfate 0.4 mg/m², cyclophosphamide 750 mg/m², and doxorubicin hydrochloride 10 mg/m²), in addition to 4 cycles of intrathecal methotrexate (12 mg) and 2 cycles of high-dose intravenous methotrexate (3000 mg/m²) over 6 months, as detailed in our case report. The patient only started to show signs of infection (ENT and lung) after chemotherapy. We hypothesize that chemotherapy unmasked his immunodeficiency, which may have been present throughout childhood. It is speculative whether he had transient hypogammaglobulinemia of infancy, requiring IRT. Unfortunately, there are no records or documentation available.

We thank you for bringing the typesetting error to our attention. This has been passed on to and corrected by the journal.

We mentioned that the patient had been misdiagnosed with Noonan syndrome in our case report. He had dysmorphic features, including bilateral ptosis, strabismus, a long philtrum, thin lips, bilateral clinodactyly, and musculoskeletal abnormalities. He showed no signs of cardiac malformations. Turner syndrome, which results from a complete or partial loss of one X chromosome, only affects females and was therefore not a relevant differential diagnosis in the case we report. The diagnostic delay for rare diseases varies from months to decades, depending on the patient’s phenotype, age, and available resources. Many patients with rare diseases remain undiagnosed for years and many even die without an accurate diagnosis [7]. The definitive diagnosis was obtained using array CGH analysis. JS was first described in 1973, after the patient was born, and has only been recognized as an IEI during the last decade. Back then, genetic testing was not widely available, although we nevertheless agree that the patient was diagnosed too late. We believe that the present case highlights the importance of early genetic testing for correct diagnosis and treatment and implementation of specific prevention measures, such as adjusting chemotherapy dosing for patients with rare diseases.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

References


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