Immunodeficiency and Lymphoma in Jacobsen Syndrome

Nigolian H[1]*, Nieke JP[1]*, Chevallier M[2], Stathaki E[3], Sloan-Béna F[3], Carminho-Rodrigues MT[3], Jandus P[1]
[1]*Division of Immunology and Allergology, University Hospitals and Medical Faculty of Geneva, Geneva, Switzerland*
[2]*Division of Oncology, University Hospitals and Medical Faculty of Geneva, Geneva, Switzerland*
[3]*Division of Genetic Medicine, University Hospitals and Medical Faculty of Geneva, Geneva, Switzerland*
[*]*Equal contribution*

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Jacobsen syndrome (JS; ORPHA:2308) is a rare disorder with an estimated prevalence of 1 in 100 000 births and a female-to-male ratio of 2:1 [1,2]. First described by Jacobsen in 1973, JS results from partial deletion of the terminal long arm of chromosome 11 (11q deletion). Clinical manifestations are diverse and are frequently associated with Paris-Trousseau syndrome, which is characterized by thrombocytopenia and platelet dysfunction [2]. The clinical presentation varies, ranging from growth and psychomotor retardation to severe facial dysmorphia, and includes malformation of the heart and of the gastrointestinal, genitourinary, ocular, hearing, skeletal, and central nervous systems. Immunological and hormonal problems may also be present [2].

We report the case of a patient with dysmorphic features, cognitive impairment, Paris-Trousseau syndrome, and transient immunodeficiency of childhood who lived with an erroneous diagnosis for many years.

The patient was the second child of a healthy nonconsanguineous Swiss couple, with no relevant family history. He was born at 32 weeks following a pregnancy complicated by intrauterine growth restriction. In the first year, he presented with failure to thrive, delayed growth, and thrombocytopenia. He started walking at the age of 2 years, and his language and speech development were significantly delayed, with consecutive intellectual disability requiring special educational support. He was short of stature, with dysmorphic features, including bilateral ptosis, strabismus, long philtrum, thin lips, bilateral clinodactyly (fifth finger), and limited elbow mobility that required surgical correction. Intravenous immunoglobulin replacement therapy (IRT, 0.4 g/kg/mo) was given for recurrent infectious tonsillitis, otitis, and bronchitis, which required regular courses of antibiotic treatment from the age of 8 until 12 years. Thereafter, no relevant infections were observed.

At the age of 46 years, he presented with dysphagia and tonsillitis resistant to antibiotic treatment. A biopsy of the right tonsil revealed high-grade B-cell lymphoma, not otherwise specified (CD20$^+$ CD79a$^+$, CD10$^+$, BCL6$^+$, EBER$^-$, CD30$^-$, IRF4$^-$, CD5$^-$, and PDL1), with a proliferation rate of the E3 ubiquitin-protein ligase MIB1 of 100%. PDL1$^+$ tingible body macrophages without necrosis were found. Rearrangements in MYC, Bcl-2, and Bcl-6 were absent. Serological analyses for active viral herpes and varicella zoster infections, EBV, CMV, parvovirus B19, HIV, and hepatitis B and C were negative.

The patient received 6 cycles of R-EPOCH chemotherapy (rituximab 570 mg, etoposide phosphate 75 mg/m^2, prednisone 60 mg/m^2, vincristine sulfate 0.4 mg/m^2, cyclophosphamide 750 mg/m^2, and doxorubicin hydrochloride 10 mg/m^2), 4 cycles of intrathecal methotrexate (12 mg), and 2 cycles of high dose intravenous methotrexate (3000 mg/m^2) over 6 months. A PET-CT scan performed during follow-up confirmed successful recovery from the lymphoma but revealed residual bronchiectasis, pulmonary infiltrates, and ground glass opacities in the lower lobe of the left lung and the apex of the right lung. The patient experienced recurrent upper and lower respiratory tract infections requiring frequent antibiotic treatments.

The biological work-up revealed thrombocytopenia, hypogammaglobulinemia, and lymphopenia with low B-cell, CD4$^+$, and CD4$^+$ $\gamma\delta$ T-cell counts (Table, see supplementary file), with no response to pneumococcal polysaccharide vaccination. Monthly IRT (0.6 g/kg) was initiated. Trough IgG levels normalized (10.9 g/L) after 3 months, and the patient reported no further infections. He is currently receiving IRT, and because of neutropenia and lymphopenia, he is receiving prophylaxis with atovaquone.

A diagnosis of Noonan syndrome had been assumed since infancy owing to his dysmorphic features, short stature, and thrombocytopenia, although this had never been confirmed by genetic testing. With the patient and his legal guardian's consent, an array CGH analysis was performed using the Human Genome CGH Microarray Kit G3 180 (Agilent Technologies) with median probe spacing of approximately 13 kb. Labeling and hybridization were performed following the manufacturer's protocols. The graphical overview was

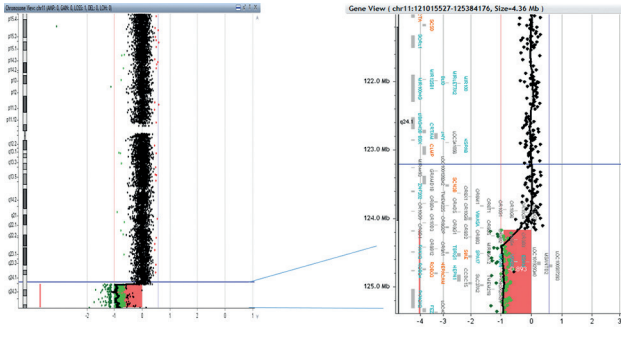

Figure. Array comparative genomic hybridization analysis showing a heterozygous terminal loss of approximately 10.7 Mb on chromosome 11 in the region q24.2q25 between positions 124170725-134927114 pb (Hg19).

obtained using Agilent Genomic Workbench 7.0.4.0, and data were analyzed using the UCSC Genome Browser Human Genome.

The array CGH analysis (Figure) revealed a heterozygous terminal loss of approximately 10.7 Mb on chromosome 11, in the q24.2q25 region, between positions 124 170 725 and 134 927 114 bp. This area encompassed 52 Online Mendelian Inheritance in Man (OMIM) genes, such as *ETS1* (ETS proto-oncogene, transcription factor) and *NRGN* (neurogranin, OMIM602350), with 18 OMIM morbid genes identified, for example, *FLI1* (friend leukemia virus integration 1, OMIM193067). Parental samples were not available.

The terminal loss on the long arm of chromosome 11, including at least 5 genes (*BSX, NRGN, ETS-1, FLI-1*, and *RICS* [*ARHGAP32*]), is compatible with JS (OMIM 147791).

JS has recently been recognized as a primary immunodeficiency [3-6]. It is often associated with recurrent respiratory, urinary, and ENT infections [1]. JS is characterized by antibody deficiency, impaired response to pneumococcal polysaccharide vaccination, and features of combined immunodeficiency. Late onset of the clinical symptoms of immunodeficiency has been reported. Antibiotic prophylaxis and IRT may be necessary to control recurrent infection. The genes involved in immune regulation are suppressed in 11q deletion syndrome. The deletion on chromosome 11 in the patient we report comprised 52 OMIM genes, including 11 genes of pathological significance, such as *ETS1*, *NRGN*, and *FLI1*, a proto-oncogene involved in platelet function whose deletion is associated with Paris-Trousseau syndrome. Ets1 knockout mice show significant defects in T, B, and NK cell development. Based on the patient's medical history, which included recurrent infections requiring antibiotic treatment and IRT from age 8 to 12 years, we assume that the patient already had immunodeficiency during childhood. We further hypothesize that chemotherapy exacerbated this immunodeficiency. Unfortunately, laboratory values prior to chemotherapy were not available.

While there are no reports on the association between JS and neoplasia in the literature, 11q deletions have been associated with myeloid and lymphoid neoplasia, especially Burkitt-like (MYC-negative) lymphoma [7]. *ETS1* may play a role in malignant transformation of hematopoietic neoplasms, including B-cell malignancies [8]. The occurrence of these 2 unusual diagnoses (JS and B-cell lymphoma) could be incidental, although an association between chromosome 11q deletion and malignancies is plausible [7,9,10].

We believe that JS patients should be screened for immunodeficiency at diagnosis and during follow-up to prevent recurrent infections. The elevated risk of Burkitt-like lymphomas in patients with the 11q deletion necessitates a high degree of vigilance.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Peter Jandus
Division of Immunology and Allergology
University Hospitals and Medical Faculty of Geneva
Rue Gabrielle Perret-Gentil 4
CH-1205 Geneva, Switzerland
E-mail: peter.jandus@hcuge.ch