

Diffuse large B-cell lymphoma chemotherapy reveals a combined immunodeficiency syndrome in cartilage hair hypoplasia

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Summary

Cartilage hair hypoplasia (CHH) is a rare autosomal recessive ribosomopathy characterised by skeletal and integumentary system manifestations. It may also present with varied forms and intensities of haematopoietic and/or immune disorders. We report a 27-year-old female who presented a picture of combined immunodeficiency after receiving an adriamycin-based chemotherapy regimen followed by autologous stem cell transplantation. Her medical history indicated neonatal dwarfism, recurrent ear, nose and throat and respiratory infections, and hypogammaglobulinaemia, which were suggestive of a primary minor B-cell immune deficiency. Taken together, the diagnosis of cartilage hair hypoplasia was suspected and confirmed by means of molecular biological analysis. Here, we discuss the causal relationship and molecular mechanisms existing between both primary immunodeficiency and lymphoma conditions and between chemotherapy cytotoxicity and aggravation of the immune system and associated haematopoietic dysfunction, considering the role of all these components in light of the initially undiagnosed cartilage hair hypoplasia. Finally, this case highlights the importance of screening for primary immunodeficiencies in the setting of a diagnosis of lymphoma and/or dwarfism; moreover, CHH must be distinguished from other causes of small size; its diagnosis and complete check-up must include the molecular characterisation, and its management must be global in collaboration with haematologists, immunologists and internists.

Key-words: cartilage hair hypoplasia, primary immune deficiency, secondary immune deficiency, lymphoproliferative disorder, ribosomopathy

Introduction

Cartilage hair hypoplasia (CHH), is a rare autosomal recessive ribosomopathy related to a mutation in the ribonuclease mitochondrial RNA processing (*RMRP*) gene, which encodes the mitochondrial portion of the RNA processing endonuclease [1]. Apart from its skeletal and integumentary system manifestations [2], CHH may also present with

varied forms and intensities of haematopoietic and/or immune disorders [3–5]. These unfamiliar associations are little-known by the medical community, so the importance of distinguishing CHH from other causes of dwarfism may not be perceived.

Here we report the case of an initially insidious and then chemotherapy-aggravated primary immunodeficiency syndrome in the context of diffuse large B-cell lymphoma. This finally revealed CHH whose clinical presentation, excepting skeletal manifestations, was initially mild. We discuss the causal relation and molecular mechanisms existing between both primary immunodeficiency and lymphoma, those between chemotherapy cytotoxicity and aggravation of immune dysfunction, considering all these components in the background of initially unrecognised CHH.

Case report

A 27-year-old female was referred to our department for management of an autoimmune haemolytic anaemia. Recent medical history included a diffuse large B-cell lymphoma at the age of 20 with negative Epstein-Barr virus (EBV) serology. She was considered in remission after four courses of rituximab, adriamycin, cyclophosphamide, vincristine, bleomycin, prednisone and intrathecal methotrexate, and consolidation with 2 infusions of methotrexate followed by successful autologous stem cell transplantation. During and after chemotherapy she had many bacterial infections and two episodes of herpes zoster reactivation. Examination of her childhood medical history found neonatal dwarfism and scoliosis with spinal osteosynthesis (fig. 1A), recurrent acute pulmonary and ear, nose and throat (ENT) infections with otitis media from the ages of 3 to 10 years, requiring placement of tympanostomy tubes at the age of 6 and adenoidectomy. The patient described frequent bronchitis and sinusitis requiring antibiotic courses two or three times a year, complicated by bronchiectasis (fig. 1B).

The clinical examination of the patient was unremarkable, except for short-limb dwarfism (height 130 cm, weight 42 kg), fine thin light hairs and mild hypermobility of

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large joints. Biological tests matched the criteria for autoimmune haemolytic anaemia, with positive Coombs tests for warm IgG and complement C3d marking, severe hypogammaglobulinaemia (2.0 g/l) and both B and CD4+ T cell lymphopenia. Retrospective measurement of gammaglobulin found that low levels (3.5–4 g/l) were present prior to chemotherapy. **Figure 2** shows all previous and recent biological results. A low CD4 count of 209/mm³ was observed beginning at the age of 23 years (3 years after the chemotherapy), with a CD4/CD8 ratio greater than 1 and a normal total lymphocyte count. Monitored lymphocyte counts indicated a shift in the CD4/CD8 ratio to 0.6 and undetectable levels of CD19. Additionally, naïve T cells were undetectable, and the naïve B cell count was increased. On the basis of all the immunological findings, a primary immunodeficiency syndrome and a probable combined immunodeficiency syndrome were determined to

have preceded the lymphoproliferative disease, and have been secondarily aggravated by chemotherapy. Finally, from the whole clinical picture, a diagnosis of cartilage hair hypoplasia, which is commonly associated with various immune dysfunction disorders, was made and confirmed with the identification of heterozygote mutation of the *RMPR* gene (substitutions 214 A>T, 230 C>T). The autoimmune haemolytic anaemia was then effectively treated with steroids as well as supportive intravenous immunoglobulin and oral prophylaxis with sulfamethoxazole-trimethoprim and valaciclovir.

A primary EBV infection was found with a progressively increasing viral load, requiring treatment with anti-CD20 antibodies. She later experienced acute episodes of neutropenia and lymphopenia, without criteria for lymphoproliferation on osteomedullar biopsy, as well as a cutaneous sarcoidosis-like granulomatous disorder without positive tests for infectious causative agents, such as rubeola. Cul-

Figure 1: Chest X-ray showing scoliosis with spinal osteosynthesis and images of bronchiectasis.

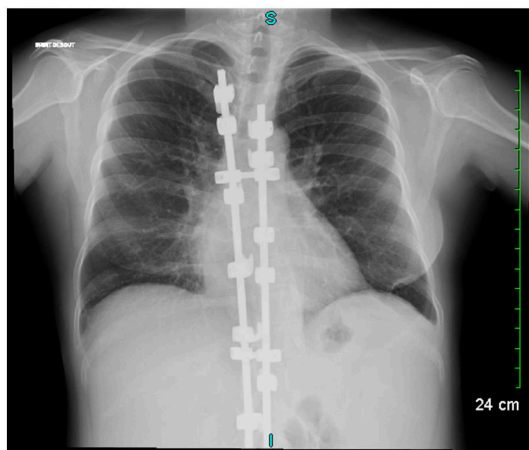


Figure 2: Thoracic computed tomography confirming the X-ray findings.

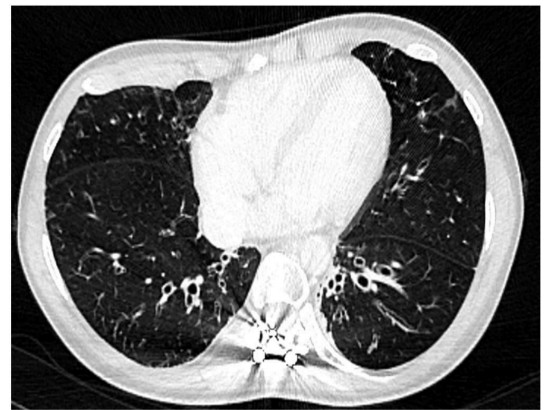


Figure 3: Clinical course and biological test results.

CLINICAL & IMMUNOLOGIC EVENTS AND Treatment applied	PRE-CHEMOTHERAPY		POST-CHEMOTHERAPY							
	RECURRENT E.N.T. & RESPIRATORY INFECTIONS		NEUTROPENIA Recombinant Granulocytes Colony Stimulating Factor							
AND Treatment applied	SLIGHT HYPOGAMMAGLOBULINEMIA AND T-CELLS ANOMALY (retrospective data)		SEVERE HYPOGAMMAGLOBULINEMIA AND T-CELLS ANOMALY Monthly Sub cutaneous Immunoglobulins (0,4 G/Kg)							
			AUTO-IMMUNE HEMOLYTIC ANEMIA Cortico steroids (1mg/kg and tapering)							
			Ebstein-Barr Virus PROLIFERATION Rituximab							
BIOLOGIC EXAMS	December 2004	January 2005	May 2013	September 2013	March 2015	Jun 2016	July 2016	August 2016	May 2017	July 2017
Hemoglobin (G/dl)	11.5	11.0	6.5	12.5	12.2	12.2	13	12	11.6	5.6
Platelets (G/l)	114	283	291	303	181	160	181	167	247	172
Neutrophils (G/l)	1.76	5.36	0.0	6.44	2.1	2.77	0.71	0.03	6.52	1.41
Lymphocytes (G/l)	0.1	0.69	0.92	0.61	0.76	0.77	0.76	1.06	0.94	0.74
CD4 + T-cells	-	-	0.49	0.155	-	0.243	0.540	0.255	-	0.161
CD8+ T-cells	-	-	0.15	0.235	-	0.177	0.366	0.410	-	0.417
NK-cells	-	-	0.05	0.120	-	0.142	0.100	0.146	-	0.06
CD19 + B-cells	-	-	0.15	0.157	-	0.071	0.100	0.0	-	0.0
Gammaglobulins (g/l)	-	4.3	3.8	2.8	-	11.5	10.7	9.9	9.7	8.2
Ig G	-	-	2.14	1.52	-	9.11	8.86	8.31	7.73	6.46
EBV load (PCR/log)	-	-	-	-	4.21	5.31	4.88	4.31	3.76	3.69

ture of medullar progenitors was not inhibited by the patient's own serum, and the medullar karyotype remained normal. Ciclosporin treatment resulted in improvement of the granulomatous signs and neutropenia.

Discussion

This case highlights the importance of screening for primary immunodeficiency syndromes and the value of considering a patient's whole medical history, including marked skeletal disorders [2], in the context of a diagnosis of lymphoma. Primary immunodeficiency and lymphoproliferative disorders may share a similar pathogenic background [6], which can alter the treatment strategy for a successful therapeutic option, including allogenic bone marrow transplant, in the context of CHH [7].

CHH is pleiotropic in both its physical signs and resulting immune dysfunctions, and is associated with an increased predisposition to malignancies, especially non-Hodgkin's lymphoma and basal cell carcinoma [6]. In our patient, the initial clinical presentation of immune dysfunction corresponded to that of a slight B-cell immunodeficiency, although retrospective blood analysis found some T-cell anomalies. Secondly, after chemotherapy, the clinical presentation had features of combined immunodeficiency, with relapsing or persistent and complicated herpesviridae infections, granulomatous disorders [8], autoimmune events [5], some cytopenias with no proven immune dysfunction mechanisms. Immune dysfunction should be considered specifically in relation to the aggravated abnormal myelopoiesis in CHH. Some of the administered cytotoxic drugs could have played a role in the aggravated profile of both immunodeficiency and haematopoiesis in our CHH patient.

CHH is associated with chromosomal instability leading to alterations of the mitotic spindle checkpoint [1, 9], largely due to significantly increased levels of cyclin B2 mRNA, as well as telomere dysfunction in various types of cells, including T cells [3, 8, 9]. Therefore, in addition to correction of the immunodeficiency [4, 10], reduction in the risk of relapse of autoimmunity [5] and lymphoproliferative disorders [6], mini-allografts or use of C19 CAR T cells allograft procedures that also take into account drug cytotoxicity may be considered first/second-line treatments in haematological manifestations of CHH [7, 11–13]. Early diagnosis of CHH / primary immune deficiency in childhood would have allowed her to receive an allograft, in order to avoid opportunistic infections, autoimmunity and prevent the known risk of lymphoma by correction of the T-cell defect in CHH [3], even though long term outcome after allografts in CHH patients remains unknown.

Finally, paediatric and adult specialists must be made aware of the important immuno-haematological aspects of CHH beyond its skeletal effects, which must be distinguished from other causes of small size. The diagnosis and full investigation must include the molecular characterisa-

tion, and management and follow up must be a collaboration with haematologists, immunologists and internists.

Disclosure statement

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