A Case of Uveitis in a Patient With Juvenile Myelomonocytic Leukemia Successfully Treated With Adalimumab

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Summary: Patients with juvenile myelomonocytic leukemia due to germline *CBL* mutation (10% to 15%) may have a subacute course occasionally associated with autoimmune disorders, which may resemble RAS-associated autoimmune lymphoproliferative disorder. In both conditions, prognosis and standard treatment for autoimmune phenomena remain poorly understood. We report the case of a 7-year-old boy with juvenile myelomonocytic leukemia with severe steroid-dependent uveitis, who did not respond to several therapeutic attempts with immunosuppressant agents, including sirolimus, and was finally successfully treated with adalimumab. This case offers further insight into the management of autoimmune disorders in the context of predisposing genetic conditions.

Key Words: JMML, RALD, CBL, RAS, autoimmune, uveitis, adalimumab

Juvenile myelomonocytic leukemia (JMML) is a clonal proliferation of hematopoietic stem cells, typical of early childhood, representing about 2% to 3% of children leukemias.[1] The diagnosis requires the presence of all the major criteria (splenomegaly, persistent peripheral monocytosis, <20% of blasts in the bone marrow and/or in the peripheral blood and absence of the BCR-ABL fusion gene), associated with at least 1 among the category 2 criteria (somatic mutations in RAS or *PTPN11*, clinical or genetic diagnosis of neurofibromatosis 1 or germline *CBL* mutation with loss of heterozygosity in blood cells), or 1 of the category 3 features (including chromosomal abnormality, circulating myeloid or erythroid precursors, increased hemoglobin F for age, hyperphosphorylation of STAT5 or granulocyte-macrophage colony stimulating factor hypersensitivity). Cells from affected patients display an abnormal sensitivity to granulocyte-macrophage colony stimulating factor, rising from pathologic activation of the RAS signaling pathway by mutations of any of the JMML-associated genes (*NRAS*, *KRAS*, *NF1*, *PTPN11*, or *CBL*).[1]

JMML is fatal when untreated, with up to 30% of patients progressing to acute myeloid leukemia[2,3] and most children dying from progressive respiratory and multiorgan failure. Different therapeutic options are reported, stem cells transplantation (hematopoietic stem cell transplantation) being the only curative one, although burdened with a very high relapse rate (35% to 40%).[4]

However, cases have been described of JMML with an indolent clinical course, characterized by spontaneous regression of proliferative myelomonocytic disease and persistence of autoimmune disorders, B lymphocytosis, and RAS-mutated clones.[5] Some authors consider indolent forms of JMML as a distinct disease, sharing features with both apoptosis deficiency disorders (namely autoimmune lymphoproliferative syndrome) and malignances. The similarities with these conditions consist, respectively, on the development of lymphoproliferation and autoimmunity and on the risk of malignant transformation, imposing a close hematologic follow-up. Indolent JMML recognizes different possible genetic backgrounds, converging in the general definition of RASopathies. They comprise a group of clinically distinct disorders due to germline mutations in genes involved in the RAS-MAPK signaling pathway, which regulate cell division and differentiation: they include Noonan syndrome, neurofibromatosis 1, Costello syndrome, cardiofaciocutaneous syndrome, and Legius syndrome. RAS-associated autoimmune lymphoproliferative disorder (RALD) is probably the most known form.

Few cases have been described of indolent JMML or RALD with associated *CBL* mutations and knowledge is lacking about the occurrence of autoimmunity and the long-term course of disease. We contribute to the knowledge on this issue by reporting a case of uveitis in a patient with JMML successfully treated with adalimumab.

CASE REPORT

A 7-year-old boy was referred to our Pediatric Rheumatology Unit for severe steroid-dependent uveitis. The boy was diagnosed at the age of 2 years with JMML, based on the association of hepatosplenomegaly, persistent monocytosis (monocyte count, 900 to 1240 cells/mcL), evidence of blast cells in the bone marrow and *CBL* mutation with somatic loss of heterozygosis in blood cells confirmed by Sanger sequencing (courtesy of Professor Zecca, Paediatric Haematology Oncology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy): the disease displayed an indolent course, not requiring any treatment (see Table 1 for laboratory values). At the age of 3, he developed severe bilateral steroid-dependent uveitis with steroid-induced hypertension and cataract (prednisone, 0.5 to 1 mg/kg/d). Methotrexate (15 mg/m^2/wk) was started as a steroid-sparing agent but discontinued because of an infectious pneumonia. Emphasizing the indolent course of his hematologic disease and the involvement of *CBL* in the RAS-mammalian target of rapamycin (mTOR) pathway, we proposed a trial with sirolimus (1.5 mg/m^2/d), an mTOR inhibitor previously proved effective in both primitive uveitis[6] and autoimmune manifestations associated with JMML.[7] However, after 2 months of treatment, despite the achievement of an adequate blood concentration of the drug (13.4 ng/mL) and the association of topical steroids, the uveitis did not show any improvement, neither the monocyte count decreased (monocyte count, 1800 cells/mcL). Therefore, sirolimus was discontinued and

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TABLE 1. Laboratory Values of a Boy With JMML and Associated Autoimmune Uveitis and Administered Drugs

Age (y)	WBC ($\times 10^6$/L)	Hb (g/dL)	Platelets ($\times 10^6$/L)	Monocytes ($\times 10^6$/L)	Eosinophils ($\times 10^6$/L)	Uric Acid (mg/dL)	LDH (U/L)	Spleen Length (cm)	Ongoing Therapy
3	6480	9.1	121,000	800	200	4.4	184	11.8	None
4	11,130	11.3	296,000	1000	630	3.3	189	—	Topical and systemic corticosteroids
4	9350	12.3	229,000	1000	390	—	—	—	Topical and systemic corticosteroids
5	9270	12.6	336,000	1500	500	3.6	179	—	—
7	10,390	12.6	254,000	1100	460	—	—	—	Topical and systemic corticosteroids
8	8270	12.6	247,000	1800	640	—	—	—	Sirolimus and topical corticosteroids
8	7080	12.5	210,000	900	440	—	—	—	Methotrexate
8	7580	12.8	255,000	700	370	—	—	—	Methotrexate and systemic corticosteroids
9	8290	13.1	156,000	1070	510	—	—	15	None
9	8970	12.7	259,000	960	290	—	—	16	Mycophenolate
10	7620	12.7	232,000	910	160	4.4	136	—	Adalimumab

Hb indicates hemoglobin; JMML, juvenile myelomonocytic leukemia; LDH, lactic dehydrogenase; WBC, white blood cells.

other attempts were made with methotrexate (15 mg/m^2/wk) and subsequently mycophenolate mofetil (500 mg twice a day), along with a further course of topical and systemic corticosteroids (prednisone 0.5 mg/kg/d). Thereafter, once ruled out the presence of adjunctive cytogenetic abnormalities, a therapeutic attempt with adalimumab, a fully human anti-tumor necrosis factorα monoclonal antibody, was proposed, at the dose of 40 mg once every other week subcutaneously. Six months later, his uveitis showed complete remission, allowing to discontinue both systemic and topical corticosteroids.

DISCUSSION

Germline *CBL* mutation is one among the most recently described in JMML[8] and is estimated to be detectable in 10% to 15% of affected patients[9]: it consists of an ubiquitin ligase, acting as a negative regulator of several signaling pathways, including RAS-MAPK. Similarly to cases with germline mutations of *PTPN11* (typical of Noonan syndrome), forms of JMML with mutations of *CBL* tend to display an indolent behavior, often achieving spontaneous regression. Patients usually display a complex clinical picture tentatively described as "CBL syndrome" or "Noonan syndrome-like disorder with or without juvenile myelomonocytic leukemia (NSLL)," which comprises: typical facies (thin and sparse hair, broad forehead, hypertelorism, mild ptosis and downslanting palpebral fissures, deeply grooved philtrum and broad nasal bridge, thick lips, low set, and posteriorly rotated ears) reminiscent of the facial gestalt of Noonan syndrome,[10] growth and developmental retardation, attention deficit and hyperactivity disorder, hyperpigmented skin lesions, joint laxity, cardiovascular abnormalities, and cryptorchidism.[11] If loss of heterozygosity occurs in somatic tissues, leading to acquired uniparental disomy of 11q23, CBL syndrome is likely to predispose to development of malignancies.[12,13]

The association with autoimmune phenomena reported in 14% to 22% of cases of JMML[14] poses a diagnostic dilemma in the differentiation between indolent JMML and RALD.

In fact, a large majority of patients with RALD meet the revised diagnostic criteria for JMML, yet it is to be established whether RALD is a nonmalignant disease, a premalignant condition, or a clonal indolent malignancy of childhood. The definitive differential diagnosis among RALD and JMML relies on the evidence of cytogenetic abnormality (eg, monosomy 7), which excludes RALD, suggesting a malignant process. However, normal bone marrow cytogenetics is also reported in ~65% of patients with JMML. Although common RAS mutations are found in RALD and JMML, the latter is apparently characterized by the accumulation of additional genetic abnormalities contributing to the malignant phenotype.[15]

In both conditions, due to the paucity of cases, prognosis and standard treatment for associated autoimmune diseases remain poorly understood.[16]

The most common autoimmune manifestations reported to date in association with RALD and JMML (Table 2) include those typical of the autoimmune lymphoproliferative syndrome, consisting either in hemolytic anemia or thrombocytopenia. Several cases have also been described of autoimmune vasculitis, among which 4 associated with *CBL* mutations. In another patient carrying a *CBL* mutation, a moyamoya vasculopathy was observed. In 2 distinct cases of *KRAS* mutation, recurrent Henöch-Schonlein purpura and systemic lupus erythematosus were reported, respectively. Similarly, in a case of indolent JMML, lupus nephritis along with arthritis, Raynaud's phenomenon and Hashimoto thyroiditis have been described. Moreover, in one patient with *NRAS* mutation episodes of thrombotic thrombocytopenic purpura were signaled. The latter resolved after several therapeutic attempts with the administration of sirolimus, an inhibitor of mTOR, involved in the RAS signaling pathway.[7]

To our knowledge, this case represents the first report in the literature of autoimmune uveitis in association with indolent JMML. Our patient failed to benefit from several therapeutic attempts with immunosuppressant agents, such as methotrexate and mycophenolate mofetil. On the basis of the reported efficacy of sirolimus in the above-mentioned case of thrombotic thrombocytopenic purpura, as well as in cases of uveitis, we undertook a trial with this agent, which however failed to yield the expected result. Instead, our patient displayed a surprising response to adalimumab, achieving persistent remission, which is still maintained to date, after a 6-month follow-up. To our knowledge, adalimumab had been previously used in only 1 patient carrying a mutation in *KRAS* with a clinical picture comprising immune

TABLE 2. Review of the Literature

Disease	No. Cases	Autoimmune Disease	Therapy	References
JMML	1	Lupus nephritis, arthritis, Raynaud phenomenon, Hashimoto thyroiditis	—	Kitahara et al[17]
RALD	1	Pericardial effusion	—	Calvo et al[15]
RALD	1	Coombs positive hemolytic anemia and thrombocytopenia	Blood product transfusions, IVIG, and corticosteroids	Levy-Mendelovich et al[18]
RALD	1	Pancytopenia and thrombocytopenia	—	Shiota et al[19]
RALD	1	Anemia	—	—
RALD	1	Recurrent migratory cutaneous erythematous plaques	Topical corticosteroids	Giacaman et al[20]
CBL	4	Vasculitis	—	Niemeyer et al[8]
CBL	1	Moyamoya	—	Hyakuna et al[21]
CBL	2	Polyclonal gammopathy	—	Pathak et al[22]
KRAS	1	Immune thrombocytopenia, recurrent Henöch-Schonlein purpura, and intestinal Behçet disease	Prednisone, cyclosporine, adalimumab	Moritake et al[23]
KRAS	1	Rosai-Dorfman syndrome and systemic lupus erythematosus	Prednisone, methotrexate mercaptopurine, rituximab, intravenous cyclophosphamide, azathioprine, and mycophenolate mofetil	Ragotte et al[24]
NRAS	1	Thrombotic thrombocytopenic purpura	IVIG, prednisolone, red blood cells and platelet transfusions, fresh frozen plasma, plasma exchange, rituximab, cyclophosphamide, sirolimus	Maschan et al[7]

Cases of RASopathies with associated autoimmune disorders and administered treatments.
CBL indicates Casitas B-lineage lymphoma; IVIG, intravenous immunoglobulins; JMML, juvenile myelomonocytic leukemia; KRAS, Kirsten RAt Sarcoma viral oncogene; NRAS, neuroblastoma RAS viral oncogene; RALD, RAS-associated lymphoproliferative disease.

thrombocytopenia, recurrent Henöch-Schonlein purpura and intestinal Behçet disease. There are no previous reports about the administration of adalimumab in autoimmune conditions associated with JMML.

CONCLUSIONS

To our knowledge, this is the first report about the administration of a tumor necrosis factor-antagonist in an autoimmune condition occurring in JMML.

The correct therapy for an autoimmune disease in the context of a predisposing genetic condition can represent a difficult challenge. For considerations of safety, we first chose to treat uveitis with drugs conventional for JMML, and only after their failure we switched to a medication approved for autoimmune uveitis irrespective of genetic background.

Further studies are needed to set the efficacy and safety of adalimumab in these clinical settings, although their performance could be hampered by the paucity of affected patients.

We believe that it is important to take stock of single experiences about autoimmune disorders associated with RASopathies, particularly in cases where crossover therapies are not obvious.

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