Low-dose sirolimus in two cousins with autoimmune lymphoproliferative syndrome-associated infection

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Autoimmune lymphoproliferative syndrome (ALPS) is characterized by non-malignant lymphoproliferation and autoimmunity, with a wide spectrum of clinical manifestations (OMIM 601859). Typical features include enlarged spleen and lymph nodes and autoimmune cytopenia. We describe a family with ALPS in which two cousins independently presented to their physicians with infection and discuss the therapeutic potential of sirolimus.

Case reports

Case 1

Patient 1, a boy, presented at 16 months of age with a bacterial pneumonia. Laboratory data indicated severe neutropenia, mild anemia, increased monocytes and hypergammaglobulinemia. In addition, clinical examination indicated splenomegaly and enlarged neck and inguinal lymph nodes. Peripheral blood and bone marrow analysis ruled out a diagnosis of juvenile myelomonocytic leukemia, while raised double-negative T cells (DNT) and genetic analysis (mutation c.575dupG p.E194Gfs*18 in *FAS*) confirmed a diagnosis of ALPS.

Two weeks later, a further bacterial infection occurred, again associated with neutropenia, and low-dose sirolimus was given (0.5 mg/day = 1 mg/m^2 daily; trough level, 5.7 ng/mL; therapeutic range, 4–2 ng/mL), leading to an almost complete normalization of hematologic parameters (Table 1) and to progressive shrinking of the spleen and lymph nodes. At 3 year follow up with intermittent use of low-dose sirolimus, no new bacterial infection had occurred and clinical conditions remained good, with no adverse effect of the drug.

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Case 2

Patient 2 was the cousin of patient 1. From the first year of life, she had repeated episodes of otitis media, often perforated, with more than two episodes per month. Given that she also had an episode of bacterial pneumonia, her doctor had prescribed anti-pneumococcus vaccination and amoxicillin prophylaxis, but without appreciable benefit. At the age of 6 years, clinical examination indicated enlarged neck lymph nodes and video-endoscopy showed that her adenoids were blocking 75% of the airways. Considering the clinical history in her cousin, immunological and genetic analyses confirmed a diagnosis of ALPS. Hypothesizing that lymphoproliferation could likely be the basis for recurrent otitis, and upon receiving informed consent by the parents, we proposed a trial with sirolimus (1 mg/day = 1.3 mg/m^2 daily; trough level, 4.3 ng/mL). During 6 months of treatment, the patient had only three episodes of otitis, compared with 13 in the same period the previous year. More strikingly, we observed a dramatic and progressive shrinking of the adenoids, with a reduction of airway obstruction from 75 to 60% and to 45% after 1 and 2 months of treatment, respectively (Fig. 1). Otitis media with perforation developed again 4 months after the interruption of sirolimus, but a second course of the drug led to remission over 2 years of follow up.

Discussion

Recurrent otitis media is a common problem in preschool children, usually not requiring any specific immunological investigation. Primary immunodeficiency disease should be considered, however, when other infectious or lymphoproliferative symptoms are present, or when high recurrence persists into school age. Although the association of ALPS with adenoidal hypertrophy and recurrent otitis has previously been described, this is not the typical clinical presentation of the disease.[1] Of note, patient 2 did not have an enlarged spleen, and the symptoms would have been easily overlooked if a family history of ALPS had not already been noted.

Table 1 Clinical and laboratory data

	Patient 1		Patient 2	
	Presentation	Follow up	Presentation	Follow up
Age	16 months	32 months	5.9 years	6.8 years
RBC (cells/μL)	4 100 000	532 000	4 320 000	4 590 000
Hemoglobin (g/dL)	**9.0**	12.3	11.2	12.6
Lymphocytes (cells/μL)	3,270	5,100	2,200	1,400
Neutrophils (cells/μL)	**270**	2,400	1,700	2,500
Esosinophils (cells/μL)	210	230	340	280
Monocytes (cells/μL)	**1,070**	800	200	300
PLT (*n*/μL)	244 000	253 000	242 000	204 000
CRP (mg/L)	**135**	0.6	0.8	2.4
ESR (mm/h)	**120**	**40**	17	15
IgG (mg/dL)	**1,580**	1,189	1,078	1,224
IgA (mg/dL)	**239**	106	163	198
IgM (mg/dL)	**199**	108	142	39
LDH U/L	**1,415**	313	276	194
AST (IU/L)	**136**	32	26	35
Vitamin B12 (pg/mL)	**7,470**	**5,608**	**4,832**	**2,040**
Sirolimus ng/mL (therapeutic range 4–12 ng/L)	–	5.7	–	4.8
Spleen longitudinal axis (cm) (Normal range for age and sex)	**12.0** (5.6–8.3)	**10.5** (5.9–9.9)	8.5 (5.7–8.9)	8.0 (6.6–10)
DNTα/β (%CD3)	**11.5**	**9.4**	**6.8**	**5.5**

Bold, beyond normal range. AST, aspartate aminotransferase; CRP, C-reactive protein; DNT, double-negative T cells; ESR, erythrocyte sedimentation rate; Ig, immunoglobulin; LDH, lactate dehydrogenase; PLT, platelets; RBC, red blood cells.

The variable clinical presentation in the two cousins should not surprise, because it is well known that ALPS is associated with both incomplete penetrance and variable clinical expression.[2]

Treatment for ALPS is usually aimed at controlling autoimmune phenomena and is based on glucocorticoids, i.v. immunoglobulins and immunosuppressive drugs. Glucocorticoids are effective but protracted use is not advisable in children. In recent years, sirolimus has become the conventional treatment for ALPS, thanks to a high rate of clinical and laboratory response.[3,4] In our experience, patients with less severe disease, who do not need urgent intervention, may have excellent response to low-dose sirolimus, which is also tolerated very well.[5] Indeed, the presence of mammalian target of rapamycin hyperactivation in ALPS may offer a biologic rationale for treatment with sirolimus.[6] For this reason, we choose to use low-dose sirolimus, obtaining a trough level at the lower end of the therapeutic range. It could be argued that adenoidectomy could have been an easier choice. The adenoid volume, however, was still below the threshold of 80% airway obstruction, which is the current trigger point for surgery, and the efficacy of adenoidectomy in recurrent otitis is not proven.

Even if a single case cannot be proof, the fact that the prompt shrinking of adenoids was paralleled by striking reduction of otitis recurrence and reduction of DNT, supports the idea that recurrent otitis in children with ALPS may be particularly responsive to treatment with sirolimus.

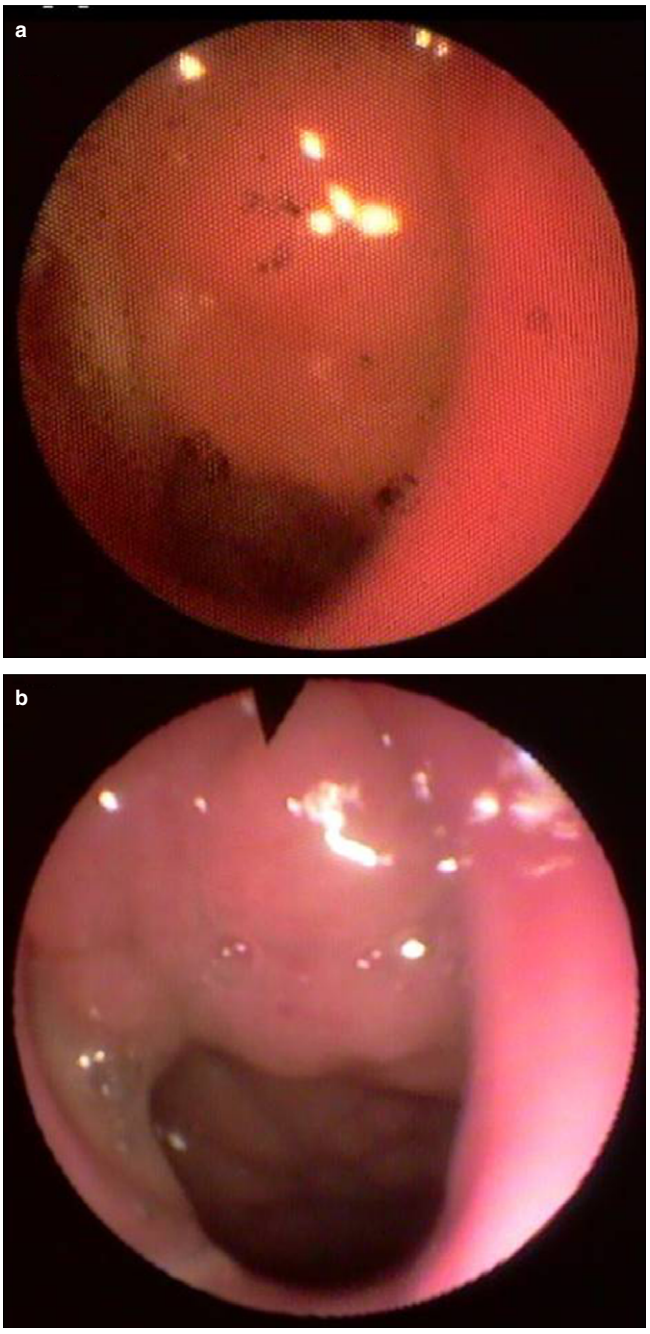

Fig. 1 Fibroscopy showing adenoids obstructing (a) 75% of the airways before treatment and (b) 45% after 2 months of sirolimus.

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Disclosure

The authors declare no conflict of interest.

Author contributions

A.N. enrolled patients and wrote the paper; E.V. coordinated the immunological laboratory studies and revised immunological content; C.L. performed immunological tests and corrected the paper; G.P. performed video-endoscopic analysis and revised the content of the paper; A.T. designed the study, and drafted and approved the paper. All authors read and approved the final version of this manuscript.

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