Systemic connective tissue disease complicated by Castleman's disease: report of a case and review of the literature

Background and objective. **Castleman's disease represents an atypical lymphoproliferative disorder characterized by the prevalence of B CD5-positive cells in the marginal zone. The occurrence of autoimmune manifestations has often been reported, but the associations of Castleman's disease with systemic autoimmune syndromes has been rarely described. Otherwise, many authors stressed the difficulties in distinguishing between connective tissue disease and Castleman's disease in most cases. To clarify this issue, we describe a patient and collected from the literature all cases of Castleman's disease associated to a connective tissue disease.** ***Case report.*** **A 19 years old woman presented with autoimmune thyroiditis and polimyositis. Seven years after the onset she developed a systemic inflammatory flare and a burst of autoimmunity, followed by generalised lymphoadenopathy. A mediastinal lymph node biopsy led to the diagnosis of Castleman disease of the mixed type. Chemotherapy was performed, with rapid response on the lymphoproliferative disorder but with persistence of underlying autoimmune disorder. The plasmatic dosage of B-lymphocyte stimulator (BLyS) was high (13.3 ng/mL) at diagnosis of Castleman's disease. It fell down dramatically after chemotherapy (4.97 ng/mL), even though it remained only just over the mean BLyS value found in healthy blood donors (3.37±0.78- ng/mL).** ***Comment.*** **Castleman's disease can present autoimmune traits. In our patient, Castleman's disease complicated the course of a connective tissue disorder several years after the onset. We hypothesize that the chronic stimulation of B cell clones, particularly CD5+, by BLyS could favour the development of both autoimmune diseases and a broad range of lymphoproliferative disorders (such as Castleman's disease). This is the first report of increased BLyS levels in a patient with Castleman's disease, supporting a possible pathogenetic role of BLyS in the development of an autoimmune disorder and of a B lymphoproliferative disorder years later.**

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Castleman's disease, or angiofollicular lymphoid hyperplasia, belongs to the atypical lymphoproliferative disorders, a heterogeneous group of diseases characterized by a hyperplastic-reactive process involving the immune system.[1,2] Among the conditions predisposing to the occurrence of atypical lymphoproliferative disorders, several reports have recorded autoimmune disorders.

We describe a case of a young woman affected by a systemic connective tissue disease, who developed multicentric Castleman's disease seven years after the onset of the autoimmune disorder, while receiving immunosuppressive treatment with cyclosporine.

Case report

In 1994, a 19 years old girl presented with a non-erosive bilateral arthritis of hands and wrists, leukopenia and hypocomplementemia. The initial diagnosis was that of undifferentiated connective tissue disease and she was treated with antimalarial drugs and low doses of corticosteroids.

One year later (1995), she presented with myositis and autoimmune thyroiditis. Further investigations revealed a systemic inflammation (ESR 44 mm/h), elevated gammaglobulins, antinuclear antibodies (ANA) with speckled pattern and anti-extractable nuclear antigens (ENA) antibodies (anti-Ro and anti-Jo1). Idiopathic inflammatory myopathy was diagnosed at this time. The patient received three daily pulses of 1 g of IV methylprednisolone, followed by oral glucocorticoid therapy at an initial dosage of 60 mg/die, then gradually tapered with clinical benefit. Nine months later, because of the poor response, she received methotrexate (15 mg/week), and one year later cyclosporine A (3 mg/kg/day) was associated. After receiving a satisfactory control on signs and symptoms ,methotrexate was stopped and cyclosporine was maintained as a monotherapy until April '01.

Four years after starting cyclosporine A therapy (April 2001), she suddenly developed high fever (39°C), neutrophilic leukocytosis (29.6×10^3/mm^3, neutrophils 91.5%), hemolytic anemia, acute renal failure (creatinine rose up to 4.4 mg/dL) with proteinuria (1,4 g/24hr), hypertension and rapid appearance of a poliserositis (pleural, pericardial and abdominal effusions). She also showed hepatosplenomegaly (maximum spleen diameter of 15 cm, longitudinal liver diameter of 21 cm). Cyclosporine A was stopped and the patient received 3 daily pulses of 500 mg of IV methylprednisolone, with immediate remission of the acute renal failure, and antibiotics for a suspected pulmonary infection, not further confirmed by the microbiologic and serologic investigations. An overlapping connective tissue disease with features of different entities had finally appeared. A treatment with high dose IV immunoglobulins (0.4 g/kg/die) was started, with some benefit.

Two months later, the patient showed a new relapse characterized by fever, diarrhoea, poliserositis, neutrophilic leukocytosis, thrombocytosis and acute renal failure with nephrotic syndrome and hypertension. Renal biopsy showed an acute interstitial and glomerular IgA nephropathy. A diffuse lymphadenopathy involving cervical, axillary and inguinal regions was noted and computerized axial tomography also revealed mediastinal and

Table 1. Laboratory findings at the time of diagnosis of Castleman's disease and at the 6th and 14th month after the first chemotherapy cycle*.

Lab. Features	*Nov '01*	*Jun '02*	*Feb '03*
White blood cells ($n\times10^3$/mm^3)	10.10	2.28	2.73
Red blood cells ($n\times10^9$/mm^3)	3.29	3.99	4.55
Haemoglobin(g/dL)	7.54	11.8	13.0
Platelets ($n\times10^3$/mm^3)	98	250	233
ESR (mm/h)	115	19	6
CRP (mg/L)	23,4	0.0	0.0
Albumine (g/dL)	2.4	4.2	4.6
Creatinine (mg/dL)	3.59	0.66	0.7
Proteinuria (g/day)	1.8	Absent	Absent
C3 (mg/dl)	83	103	67
C4 (mg/dl)	17	21	15
γ-globulins(mg/dL)	1.7	0.53.	0.6
IgG (g/L)	17.2	n.d.	6.1
ANA	Neg	1:160	1:160
Anti-DNA	Neg	Neg	Neg
Anti-ENA	Ro, Jo-1	Ro, Jo-1	Ro, Jo-1
Coomb's test	Pos	Neg	n.d.
Anti-platelets	Anti GP IIb/IIIa, Ib/IX, Ia/IIa	n.d.	n.d.
ACA-IgG	24	8	10
ACA-IgM	4	4	2
Anti-prothrombin	Neg	Neg	n.d.
Anti-β2-GPI	Neg	Neg	n.d.

aAbbreviations: ERS: eritrocyte sedimentation rate; CRP: C-reactive protein; ANA: antinuclear antibodies; anti-DNA; anti-DNA antibodieds; ENA: anti-extractable nuclear antigen antibodies; Ro: anti-Ro antibodies; Jo-1: anti Jo-1 antibodies; ACA: anti-cardiolipin antibodies; anti-prothrombin: anti-prothrombin antibodies; anti-β2-GPI: anti-β2-GPI antibodies.

Table 1. Malattia di castleman associata a connettivite.

Autore	*Sesso, Eta'*	*Castleman*	*Connettivite*	*Intervallo*	*Terapia*	*Remissione*	
						Castleman	*Connettivite*
Malattia di castleman precedente o contemporanea alla connettivite							
Suwannaroj ('93)	F, 49	MCD, PC	LES	0	COP; aza	SI	SI
Hosaka (,94)	F, 39	MC, PC	LES/SS	0	steroidi	SI	SI
	M, 60	MCD, mista	LES	0	steroidi	NO	NO
	F, 46	SCD, HV	SSc/CM	0	np	np	np
Nanki (,94)	F, 60	MCD, PC	MCTD	0	Steroidi, alchilanti	SI	SI
Day ('03)	F, 39	SCD,	Miastenia	0	chirurgica	SI	SI
Emson ('73)	F, 14	SCD, HV	Miastenia	0	Escissione incompleta	Parziale	Parziale
Pasaoglu ('94)	F, 15	MCD, mista	Miastenia	- 14‡	escissione,steroidi, plasmaferesi	SI	SI
Malattia di castleman successiva alla connettivite							
Gohlke ('97)	M, 26	MCD	UCTD	8	Steroidi, aza	SI	NO
Tavoni ('93)	F, 38	MCD, PC	SS	2	steroidi	Np	Np
Higashi ('97)	F, 54	SCD, HV	SS	7	Escissione incompleta	Parziale	Np
Ben-Chetric ('89)	M, 45	MCD, mista	AR	2	NP	Np	Np
Kurotaki ('93)3	F, 40	SCD, HV	AR	5	NP	SI	NO
Carpentier-Planchon ('01)	F, 75	MCD, PC type	Poliartrite distruttiva	2	steroidi	Parziale	Parziale
Caso descritto	F, 26	MCD, mista	Sindrome overlap (PM/LES)	7	CHOP; azatioprina	SI	NO

MCD: malattia di Castleman multicentrica; SCD: malattia di Castleman multicentrica; PC: variante plasmacellulare; HV: variante ialino-vascolare; LES: lupus eritrematoso sistemico; SS: Sindrome di Sjogren; SSc: sclerosi sistemica; CM: connettivite mista; UCTD: connettivite indifferenziata; AR: artrite reumatoide; PM: polimiosite.

Table 2. Castleman's Disease Associated with Connective Tissue Disease.

Reference	*Sex, age*	*CD*	*CTD*	*Interval CTD-CC (years)†*	*Systemic manifestation*	*Laboratory data*	*MCD therapy*	*Follow-up*
Castleman's disease preceding or contemporary to connective tissue disease.								
Suwannaroj 1999 (3)	F, 49	MCD, PC type	Suspected SLE	0	CS, lymphadenopathy, poliserositis, parotid enlargement. ANA, DNA, SSA, SSB, ACA.	AIHA Coomb's +, AITP, leukocitosis, hypoalbuminemia, proteinuria,	COP; Azathioprine and rheumatologic manifestation	Response of adenopathy
Hosaka 1994 (4)	F, 39	MCD, PC t	Suspected SLE/SS	0	Fever	Coombs test, ANA, SSA, RNP,	P	Resolution
	M, 60	MCD, mixed	Suspected SLE;	0	NP anti-DNA, ACA	AITP, ANA, RNP, P	Death	
	F, 46	SCD, HV MCTD	Suspected SSc/	0	NP ANA, ENA	NP	NP	
Nanki 1994 (5)	F, 60	MCD, PC type	MCTD	0	CS, lymphadenopathy, splenomegaly, POEMS.	Anemia, ANA, RNP, RF, hypergammaglobulinemia; HLA-DR4	P, C, Melphalan	Pharmacologic remission MCTD, MCD and POEMS
Day 2003 (6)	F, 39	SCD, HV	Myasthenia	0	Absent	Absent	Excision MyastheniaEmson	Resolution of CD and
Emson 1973 (7)	F, 14	SCD, HV	Myasthenia	0	NP	Hypergammaglobulinemia	Incomplete Excision	Partial improvement
Pasaoglu 1994 (8)	F, 15	MCD, mixed	Myasthenia	- 14‡	Lymphadenopathy	Hypergammaglobulinemia	Excision, P, PP	Improvement of CD and Myasthenia
Connective tissue disease preceding Castleman's disease.								
Gohlke 1997 (9)	M, 26	MCD	UCTD	8	CS, lymphadenopathy, hepatosplenomegaly, poliserositis, nephrosic sd, Guillain Barrè.	AIHA Coomb's +, Cryos +ANA, SMA; HLA-A1, B8, DR3	P, azathioprine (previously CsA)	Improvement, with perrsistence of autoimmune features
Tavoni 1993 (10)	F, 38	MCD,PC	SS	2	Lymphoadenopathy, fever, poliserositis, parotid swelling.	ANA, SSA, SSB, hypergammaglobulinemia	P	NP
Higashi 1997 (11)	F, 54	SCD, HV	SS	7	Absent	ANA, SSA, SSB, RF, anti-platelets; Hypergammaglobulinemia	Incomplete Excision	Partial improvement of CD
Ben-Chetric 1989 (12)	M, 45	MCD, mixed	RA	2	Lymphadenopathy, splenomegaly	Anemia, HBsAg	NP	NP
Kurotaki 1993 (13)	F, 40	SCD, HV	RA	5	NP	NP	NP	Persisting RA
Carpentier-Planchon 2001 (14)	F, 75	MCD, PC type	Destructive polyarthritis	2	CS, lymphadenopathy, hepatomegaly, POEMS	Anemia, hypoalbuminemia, hypergammaglobulinemia; HLA-B27	P	Improved articular and systemic manifestations
Descripted case	F, 26	MCD, Mixed	Overlap syndrome (PM/SLE)	7	CS, lymphadenopathy, poliserositis, organomegaly, nephrosic sd	AIHA Coomb's +, AITP, hypoalbuminemia, ipogammaglobulinemia, ANA, SSA, Jo1, ACA	CHOP;Azathioprine (previously CsA) leukocitosis, proteinuria,	Remission of CD Persisted autoimmunity

CD: Castleman's disease; MCD: multicentric Castleman's disease; SCD: solitary Castleman's disease; PC: plasma cell type; HV: hyaline-vascular type; CTD: connective tissue disease; SLE: systemic lupus erythematosus; SSc: systemic sclerosis; MCTD: mixed connective tissue disease; UCTD: undifferentiated connective tissue disease; SS: Sjogren's syndrome; RA: rheumatoid arthritis; PM: polimiositis; CS: constitutional symptoms; POEMS: polineuropathy, organomegaly, endocrinopathy, M-component, skin changes; N.P: not precised; AIHA: autoimmune hemolitic anemia; AITP: autoimmune thrombocytopenia; ANA: antinuclear antibodies; DNA; anti-DNA antibodieds; SSA: anti-SSA antibodies; SSB: anti-SSB antibodies; ACA: anti-cardiolipin antibodies; RNP: RNP antibodies; ENA: anti-extractable nuclear antigen antibodies; RF: rheumatoid factor; Cryos: cryoglobulins; SMA: anti-small muscle antibodies; Jo-1: anti Jo-1 antibodies; C: cyclophosphamide; O: vincristine; P: prednisone/prednisolone; PP: plasmapheresis; H: Hydroxydaunomycin.†Period between onset of connective tissue disease and Castleman's disease. ‡Castleman's disease preceeded connective tissue disease.

intra-abdominal nodal enlargement (2.5-3.0 cm in diameter) and a thymic mass. The thoracoscopic biopsy of a mediastinal lymph node showed a histological picture consisted with multicentric Castleman's disease of the mixed variant (hyaline vascular and plasma cell type).

Despite treatment with daily pulses of IV methylprednisolone followed by high dose steroids, in the following months the patient got worse and she was referred to our department (October '01) because of the persistent systemic flare, severe anemia, thrombocytopenia, hypoalbuminemia and frank anasarca. The laboratory showed increased gammaglobulins, positive direct Coomb's test, antiplatelets antibodies, anticardiolipin antibodies and a borderline positivity of lupus anticoagulant (Table 1). There was no monoclonal gammopathy. Serological tests for Epstein Barr Virus (EBV), human herpes virus 8 (HHV8) and human immunodeficiency virus (HIV) infections were negative, as well as the direct polymerase chain reaction (PCR) for HHV8 on peripheral and nodal mononuclear blood cells and *in situ* hybridisation for EBV on lymphoid tissue were negative. A bone marrow smear ruled out lymphomatous infiltration. CDR3-related PCR products obtained by amplifying DNA extracted from the peripheral blood mononuclear cells showed a clear polyclonal pattern. Otherwise the PCR clonality analysis, performed on the paraffin-embedded lynphonodal biopsy, showed an oligoclonal pattern (Figure 1).

In November 2001, for the severity of the clinical conditions, chemotherapy was started (CHOP: cyclophosphamide 750 mg/m^2, hydroxydaunomycin 50 mg/m^2, vincristine 2 mg and oral prednisone 100 mg/day for 5 days). She completed all 6 cycles, following the guidelines for non-Hodgkin's lymphoma. The first cycle was complicated in the 4thh day by a severe anemia (haemoglobin 3.7 g/dL) and in the 8th day by a severe thrombocytopenia (14×10^3/mm^3), suddenly corrected. There was a clinical and biologic response soon after the first cycle, with disappearance of systemic manifestations, recovery of normal renal function with complete normalization of urine sediment and blood pressure, gradual disappearance of pleural, pericardial and abdominal effusions, decrease of hepatosplenomegaly and lymphoadenopathy.

After chemotherapy, azathioprine was introduced as a long-term remission-maintaining agent. Treatment was well tolerated with only transient leukopenia. At the last evaluation, in December 2003, she is well with no evidence of the lymphoproliferative disease.

The systemic connective tissue disease still reveals itself with hypocomplementemia, positivity of antinuclear antibodies (1:160) and anti-ENA antibodies (anti-Ro and anti-Jo-1). To notice, hypogammaglobulinemia replaced hypergammaglobulinemia.

The plasmatic level of B-lymphocyte stimulator (BLyS) was determined before chemotherapy by ELISA (the antibody coated plates were kindly provided by B. Nardelli; HGS, Rockville, MD) and it was 13.3 ng/mL. After the second chemotherapy cycle it decreased to 7.99 ng/mL. At the last evaluation, July 2003, BlyS value further decreased to 4.99 ng/mL. For comparison, 52 patients with active rheumatoid arthritis had BLyS values of 4.04 ± 1.92 ng/mL and 41 healthy blood donors had levels of 3.37 ± 0.78 ng/mL

Comment

The occurrence of autoimmune manifestations, such as hemolytic anemia or thrombocytopenia, has often been reported during Castleman's disease. Associations of the latter with connective tissue diseases such as rheumatoid arthritis, Sjogren's syndrome, mixed connective tissue

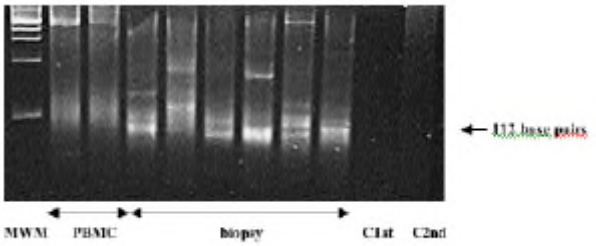

Figure 1. CDR3 PCR clonality analysis. CDR3-related PCR products were obtained by amplifying DNA extracted from the peripheral blood mononuclear cells (PBMC) and from the paraffin-embedded lynphonodal biopsy and runned on 4% agarose gel/TBE1X stained with ethidium bromide. The PBMC (done in duplicate) shows a clear polyclonal pattern, while the biopsy (6 independent amplifications) appears oligoclonal. Legend: MWM: molecular weight marker phiX HaeIII; PB: amplifications of the DNA extracted from the peripheral blood mononuclear cells; biopsy: amplifications of the DNA extracted from the biopsy; C1st and C2nd: negative controls of the first and of the second step of the semi-nested FR3 VDJ PCR (Diss et al. J Pathol 1993; 169: 291-5).

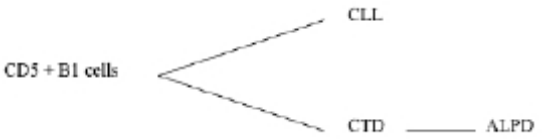

Figure 2. CLL: chronic lymphocytic leucemia; CTD: connective tissue disease; ALPD: atypical lymphoproliferative disease.

disease and myasthenia gravis have also been described.[3-14] In the literature, there's not a single interpretation of the association of Castleman's disease with connective tissue disease. Indeed, while some authors accept the coexistence of the two entities in the same patient, others assert that Castleman's disease can mimic an autoimmune syndrome, such as systemic lupus erythematosus, Sjogren's syndrome or mixed connective tissue disease, so confounding the diagnosis. Furthermore, diverse autoimmune disorders, such as rheumatoid arthritis or systemic lupus erythematosus (SLE), can present disseminated lymphadenopathy with histopathological findings compatible with Castleman's disease.[15,16] In SLE cases reported by Kojima, 6 (26%) demonstrated a histological pattern consistent with Castleman's disease. In all cases, the lymphadenopathy was noted in an early phase, generally within 12 months after the onset of connective tissue disease, and the lymph node diameter never exceeded 2.0 cm. None of the patients showed an aggressive disease course as our patient. All patients were treated with non steroid antinflammatory drugs and/or glucocorticoids and no one showed complications of the lymphoproliferative disorder during the follow-up period.[15]

Our patient had features of an overlapping systemic connective tissue disease (systemic lupus erythematosus with an initial myositic component) and, on contrary to Kojima's cases, she had a dramatic burst of a lymphoproliferative disorder which remitted only after chemotherapy. To clarify the issue of the association between Castleman's disease and autoimmune disorders, we collected from the literature all cases of Castleman's disease associated to a connective tissue disease, and divided them into two groups, based on the onset of Castleman's disease (before/contemporary or after the onset of the autoimmune disorder) (Table 2).

There's no difference of sex distribution or median age between the two groups. In both groups, multicentric

Castleman's disease of plasma cell or mixed type prevails. Even if there is only partial information on the follow-up of these patients, particularly concerning the persistence or the disappearance of autoimmunity after treatment of the lymphoproliferative disorder, some cases of contemporary onset (first group) are characterized by remission of both lymphoproliferative and autoimmune features. In the second group, on the contrary, autoimmune disease generally persists after treatment, with clinical and/or laboratory signs. It's known that B cell disorders, such as multiple myeloma, Waldestrom's macroglobulinemia, chronic lymphocytic leukemia and also Castleman's disease, can present autoimmune traits at some time during the course of the disease. Otherwise, in other cases Castleman's disease complicates the course of a connective tissue disorder after several years of follow up. In this subset, Castleman's disease is therefore secondary to the underlying autoimmune disorder, probably related to a deregulated expansion (or to a prolonged half-life) of a limited fraction of B cell clones, particularly CD5-positive ones.

It is now accepted that the autoreactive repertoire is an important component of the normal B cell population. These clones, with a natural autoantibody activity, are characterized by their widespread but low affinity binding pattern, which allows them to bind self and non-self-antigens and constitute a first barrier of defence. B cell malignancies frequently correspond to expansion of this autoreactive repertoire and, among these, chronic lymphocytic leukaemia is the most frequent type. Chronic lymphocytic leukaemia B lymphocytes are characterized by constant expression of the CD5 marker and their normal counterpart is supposed to be normal $CD5^+$ B cell located in the mantle zone of the secondary follicles.[17] Otherwise, some features of malignant B cells, such as the low amounts of surface Ig or the inability to adequately respond when stimulated through the B cell receptor pathway, suggest that they can be anergic B cells, subsequently becoming resistant to apoptosis.

The reports of common genetic factors predisposing to both chronic lymphocytic leukaemia and autoimmune diseases, the coexistence of chronic lymphocytic leukaemia and autoimmune syndromes in the same patient and the recent demonstration, in an experimental model, of 'susceptibility alleles' (the homozygous haplotype leads to chronic lymphocytic leukaemia, the heterozygous one leads to autoimmunity), suggest that there's a strong common genetic background among these pathologies.[18-20] Hence, CD5+cells should represent the crossroad between B- chronic lymphocytic leukaemia and autoimmune diseases. Along this view, Castleman's disease, an 'atypical' $CD5^+$ B cell disorder, can represent a step of the process which, starting from the normal autoreactive repertoire, leads to leuko-lymphomagenesis, perhaps through a chronic (auto)antigen stimulation.

In our reported case, the systemic connective tissue disease, presenting with overlapping features over the years that preceded the onset of the atypical lymphoproliferative disorder, could have favoured, in a genetically predisposing host, the appearance of a particular B-cell phenotype with prolonged survival, which determined the development of a lymphoproliferative disorder (Figure 2).

In this regard, we considered the expression of the newly identified B lymphocyte stimulator, BLyS, a member of the tumor necrosis factor (TNF) family which is critical for the maintenance of normal B-cell development and homeostasis.[21] Transgenic animals expressing BLyS develop a systemic-lupus-erythematosus-like disease.[22] Significant elevations of BLyS has been demonstrated in patients with SLE and rheumatoid arthritis and in Siogren's syndrome, as well as in patients with lymphoproliferative disorders, such as chronic lymphocytic leukaemia and non-Hodgkin lymphoma.[23-26] The BLyS plasmatic level found in our patient was 13.3 ng/mL. As a comparison, we considered the mean value found in a cohort of active rheumatoid arthritis patients from our division and the mean value found in healthy blood donors. After the second chemotherapy cycle, BlyS decreased to 7.99 ng/mL. At the last evaluation in July 2003 BLyS decreased to 4.99 ng/mL, value included within the 95° percentile of healthy controls. This is the first report of increased BLyS level in a patient with Castleman's disease and supports the hypothesis that a chronic inflammatory condition, through the overexpression of BLyS, could favour the development of a B lymphoproliferative disorder. Further studies are necessary to clarify the exact pathogenetic role of BLyS and to address new therapeutic approaches.

A further point to consider is that Castleman's disease occurred under cyclosporine therapy, an agent that is reported to promote EBV-associated and non associated lymphoproliferative disorders in immunocompromised patient.[27,28] Cyclosporine increases the expression of Interleukin-6, which is an important B-cell differentiation factor and has been directly implicated in the pathogenesis of several human diseases, including Castleman's disease.[29,30]

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