Springer Semin Immunopathol (1998) 20 : 425–436

Springer Seminars
in Immunopathology

Interferon-α and its effects on post-transplant lymphoproliferative disorders

Albert Faro

Pediatric Pulmonary Center, University of Florida, Health Sciences Center, PO Box 100296, Gainesville, FL 32610-0296, USA

Introduction

Post-transplant lymphoproliferative disorders (PTLDs) are a common and often fatal complication of immunosuppressive therapy. These disorders are characterized by an abnormal expansion of lymphoid cells [19, 21] and are usually associated with the Epstein-Barr virus (EBV) [20]. The incidence of PTLD varies in the different transplant populations. It is lowest in those receiving kidney transplants and highest in heart/lung transplant recipients with reports suggesting that it may be as high as 19.5% in pediatric lung transplant recipients [5, 6, 11]. Patients with PTLD may display fever, malaise, pharyngitis, lymphadenopathy, and graft dysfunction [34].

Several modes of therapy routinely used for other lymphomas, including irradiation and chemotherapy, have met with only limited success in treating PTLD. Other than reducing immunosuppression, there is no consensus on the appropriate management of this group of disorders which have a mortality rate ranging between 23–35% [6].

An imbalance in the immunoregulatory mechanism may underlie the development of PTLD as approximately half of these lesions regress when immunosuppression is reduced [5]. There is evidence suggesting the presence of a T helper type 2 (Th2) environment in PTLD [16, 29].

Interferon-α (IFN-α), a cytokine produced by many cell types including mononuclear cells, has been used by several authors to treat PTLD [16, 24, 25, 31, 38, 46, 49, 52]. It increases the lytic potential of natural killer (NK) cells, inhibits viral replication, and increases the expression of class I MHC molecules. It also modulates the immune system in a number of ways including interfering with T cells and preventing them from stimulating B cells, and augmenting the inhibition of IL-4 by IL-12. By indirectly promoting a T helper type 1 (Th1) environment in the cellular milieu, IFN-α may correct the abnormality in the patient's immune surveillance system that allows PTLD to thrive.

This chapter is divided into two main sections. The first outlines the in vitro data that provide the theoretical evidence for the use of IFN-α in PTLD. In these opening sections the mechanism of cytokine imbalance in EBV infection and PTLD will be discussed. The second summarizes the clinical evidence supporting the efficacy of IFN-α in PTLD.

Table 1. Cytokines produced by the different T helper cells

Th1	Th2
IL-2	IL-4
IFN-γ	IL-5
Lymphotoxin	IL-6
	IL-10

Table 2. Major functions of certain Th1 and Th2 cytokines

IL-2	Predominant growth factor made by Th1 cells; promotes differentiation of CD8 cells to cytotoxic T cells
Lymphtoxin	Activates neutrophils
IFN-γ	Acts on B cells and macrophages to promote opsnization and phagocytosis
IL-4	Promotes differentiation of CD4 cells to Th2; antagonizes effects of Th1 cytokines
IL-10	Inhibits cytokine production by macrophages

Cytokine regulation

Cytokines are produced by a variety of cell types including the two types of helper T lymphocytes (Th) known as Th1 and Th2 cells [15,32]. Th1 cells produce IL-2, IFN-γ and lymphotoxin. Th2 cells produce IL-4, IL-5, IL-6, IL-10, and IL-13 (Tables 1, 2). The cytokines produced by Th1 cells mediate the delayed-type hypersensitivity reaction, and those produced by the Th2 cells promote humoral responses [12, 33]. In general, Th1 cytokines promote the continued release of Th1 cytokines, while inhibiting the release of Th2 cytokines. Th2 cytokines, on the other hand, generally promote the release of Th2 cytokines and inhibit the release of Th1 cytokines.

Differentiation of naïve T cells to one or the other Th cell type is driven by the presence of either IL-12 or IL-4 [13]. IL-12 is produced mainly by activated monocytes and dendritic cells and promotes the development of Th1 cells [1]. IL-12 is a growth factor for NK cells and enhances their cytolytic activity [53]. It also causes the secretion of IFN-γ by T cells and NK cells. Receptors for IL-12 are located on NK cells, T cells and some B cells.

IL-4, on the other hand, selectively promotes the differentiation of $CD4^+$ cells to Th2 cells and antagonizes the effects of IFN-γ on a variety of cell types. It causes enlargement of individual resting B cells and increases the expression of class II MHC molecules. Most importantly, it regulates IgE-mediated responses [1]. IL-4 is produced by Th2 cells, mast cells, and basophils.

Other cytokines may be involved indirectly in the differentiation of $CD4^+$ cells into Th2 cells [22]. IL-10, a Th2 cytokine, inhibits cytokine production by macrophages and inhibits the accessory function of macrophages [1]. In addition, IL-10 appears to be an autocrine growth factor in EBV-transformed cell lines and may play a vital role in the development of lymphoproliferative disorders [4].

EBV and the immune system

EBV binds to B cells via a receptor located on the membrane, known as the type 2 complement receptor (CD21 or CR2) [37]. Normally this receptor binds C3d, a complement protein that then allows the binding of CD19, enhancing B cell proliferation. Once the virus binds, it is capped and undergoes endocytosis [50]. An immunocompetent host responds to EBV infection with an increase in NK cells, cytotoxic T cells (CTLs) and suppressor T cells [28]. These cells control not only the acute infection, but also the lifelong carrier state of the host.

Several distinct cytokines play a role in regulating the growth of EBV-infected B cells [42]. Using an in vitro system, Lotz et al. [27] demonstrated that within 24 h of infection by EBV, IFN-α is released by both NK and B cells in the absence of accessory cells. In the subsequent cascade of events IL-2 and IFN-γ are released by T cells. Thus, the host normally responds to infection by EBV with a Th1 response in an attempt to control the infection. IL-2, the major autocrine growth factor for T cells, stimulates the growth of NK cells, enhancing their cytolytic function and producing lymphokine-activated killer (LAK) cells [1]. Recently, the infusion of LAK cells was shown to be useful in the treatment of patients with EBV-positive PTLD [36].

Other cytokines studied in the context of EBV infection include IL-1, which stimulates growth in several EBV-infected cell lines [42]. IL-6 can cause the growth of EBV-infected B cells and increase the tumorigenicity of EBV-immortalized cells in athymic mice [51]. Tosato et al. [51] found that IL-6, a Th2 cytokine, was produced at high concentrations by the lesions removed from patients with PTLD. However, the levels of circulating IL-6 were only transiently elevated in these patients.

Patients with acute infectious mononucleosis have higher levels of circulating IL-10 than normal [48]. Burdin et al. [9] demonstrated that EBV-infected B cells secrete IL-10 in high concentrations. They also discovered that adding human IL-10 to B cells while they are being infected by EBV potentiated cell proliferation. The addition of anti-IL-10 antiserum inhibited cell proliferation. Of particular interest is that EBV contains a gene, BCRF1, that is homologous to the gene for human IL-10 and this viral IL10 shares in vitro activity with Th2-derived IL-10 [34]. Viral IL-10, like human IL-10 down-regulates the expression of class II MHC molecules, reducing the antigen-presenting capacity of monocytes [14] and thus down-regulating the immune system's anti-viral response.

Two clinical studies in patients with PTLD suggest the presence of a Th2 environment both systemically and in the lesion itself. Mathur et al. [29] demonstrated increased levels of IL-4 and IgE in the serum of patients with PTLD. Using qualitative reverse transcriptase-polymerase chain reaction (RT-PCR), Nalesnik et al. [35] measured cytokine mRNA levels in solid tissue specimens from patients with PTLD. IL-4 and IL-10 mRNA were present, but IL-2 and IFN-γ were not.

There is both in vitro and clinical evidence supporting the concept that EBV induces B cells to secrete cytokines that produce an environment that the virus can thrive in; a Th2 environment. The immune system's response is for T cells to release IL-2 and IFN-γ and NK cells to release IFN-α and establish a Th1 environment that will allow CTLs and NK cells to thrive and successfully combat the virus.

Interferon-α

IFN-α is composed of 12 separate proteins encoded by a family of 14 genes [42]. It has several biological actions. IFN-α increases the expression of class I MHC molecules and inhibits the expression of class II MHC molecules. It also increases the lytic potential of NK cells. In addition, IFN-α causes cells to secrete enzymes that inhibit viral replication. IFN-α can also prevent cellular proliferation. Lastly, IFN-α is an immunoregulatory cytokine that stimulates the production of some cytokines and inhibits the production of others [2, 3, 40, 43, 44, 55].

Because of these multiple biological actions, IFN-α has been studied in a variety of disorders. Although its anti-viral effects were initially discovered in the late 1950s, it is only relatively recently that recombinant DNA technology has allowed IFN-α to be produced in sufficient quantity for large clinical studies. Perhaps, its most significant effect as an anti-viral agent is in the treatment of hepatitis B and C. Studies report a positive response in 40–80% of patients treated with IFN-α [10]. Other viruses that may respond to therapy with IFN-α include papilloma viruses, herpes keratitis (in combination with acyclovir), and rhinoviruses [10].

Researchers have also examined the efficacy of IFN-α in cancer therapy [18]. Chronic myelogenous leukemia, myeloma, hairy cell leukemia, Kaposi's sarcoma, lymphomas, and melanomas are some of the malignancies known to respond to therapy with IFN-α [26]. IFN-α may exert its anti-neoplastic effect through any one of the following mechanisms: its anti-proliferative effect on tumor cells, its inhibition of angiogenesis, its inhibition of oncogene expression, or its activation of the immune system to attack tumor cells [54].

IFN-α modulates the immune system in a manner of ways. Brinkmann et al. [7] studied the effect of IFN-α on T cell's ability to help B cell differentiation in vitro. They found that when human or murine T cells were activated in the presence of IFN-α the co-cultured B-cells could not produce IgM, IgG, IgA, or IgE. The authors hypothesized that IFN-α interfered with T cell activation during the period that the cells acquire the potential to stimulate B cells. They also activated the T cells in the absence of IFN-α and then added it when the cells were cultured with the B cells. This did not suppress B cell production, suggesting that IFN-α does not act on B cells directly, but on the T cell activation process.

IFN-α also seems to directly affect the concentrations of other cytokines or of their receptors. For instance, IFN-α causes reduced IL-6 binding to its receptor in a human multiple myeloma cell line, likely by reducing IL-6 receptor density [3, 45]. In human monocytes, IFN-α decreases the steady state levels of IL-8 and epithelial neutrophil activating 78 (ENA-78) protein [44]. Parronchi et al. [40], using allergen-specific T cell clones that normally produce high levels of IL-4 and IL-5 (Th2 cytokines), demonstrated that in the presence of IFN-α these cells shifted their lymphokine production to IFN-γ (Th1 cytokine).

Several studies have confirmed that IFN-α can promote Th1 development [7, 8, 39], although the mechanism has not been entirely elucidated. Wenner et al. [55] used a T cell receptor (TCR) transgenic system to study the effects of IFN-α on T cell development. They found that IFN-α does not directly induce Th1 development, but that it does augment inhibition of IL-4 by IL-12. In other words, IFN-α seems to promote an environment that is unfavorable for the production of Th2 cytokines, but is favorable towards the production of Th1 cytokines.

IFN-α and EBV

In 1976, Menezes et al. [30] demonstrated that IFN-α is able to prevent EBV infection in treated B cells. Since then, multiple studies have examined the relationship of IFN-α and EBV infection. Lotz et al. [27] documented that B cell proliferation and immunoglobulin secretion in EBV-infected cells in vitro are regulated by recombinant human IFN-α. In addition, the effects on EBV-induced proliferation among the IFNs varied with time of administration. Maximal reduction by IFN-α was noted when it was given prior to EBV infection or simultaneously. Garner et al. [17] used an in vitro system in which unfractionated cord blood mononuclear cells, T cell-depleted cord blood mononuclear cells, or adult T cell-depleted mononuclear cells were exposed to IFN-α prior to incubation with EBV. EBV-induced B cell outgrowth was inhibited at pharmacologically achievable concentrations of IFN-α [17].

Another study examined EBV replication in the Burkitt's lymphoma-derived Daudi cell line, which is latently infected with EBV [47]. In this study the authors demonstrated that IFN-α inhibited the induction of EBV replication by 12-*O*-tetradecanoylphorbol 13-acetate (TPA) and sodium butyrate, agents that normally induce viral replication. Using Northern blotting they also showed that IFN-α reduced the levels of RNA from the *Bam*HI M and *Eco*RI E regions of the EBV genome. In other words, the mechanism by which IFN-α limits EBV replication may be at the level of transcription.

Other mechanisms to explain the effects of IFN-α on EBV have been proposed. IFN-α may cause an interruption at the level of viral binding and uptake. As stated in the section on EBV, EBV binds to the B cell via the CD21 receptor. Delcayre et al. [15] demonstrated that IFN-α prevents viral uptake by inhibiting the mobility of the CD21-EBV complex. Thus, the effects of IFN-α on EBV in vitro may occur at multiple sites.

IFN-α and PTLD

Although there are no placebo-controlled clinical trials suggesting that IFN-α may be effective in the treatment of patients with PTLD, several case reports promulgate promising results [16, 24, 25, 31, 38, 46, 49, 52] (Table 3). The first such report came from Shapiro et al. [46]. They reported on five immunocompromised patients with B cell lymphoproliferative disorder (BLPD). Two had received bone marrow transplantation, two had common variable immune deficiency and the fifth patient had chronic sinusitis. All five patients were critically ill at the time of starting IFN-α (2×10^6 IU/m^2 body surface area per dose every day for 1 week followed by three times per week) and intravenous gamma globulin (IVIg) (400–500 mg/kg per day for 3 days and then every 1–3 weeks). One of the bone marrow transplant recipients received 21 days of IFN-α therapy before succumbing to cytomegalovirus (CMV) pneumonitis. The second patient had complete resolution of her PTLD. The three patients who were not transplant recipients had complete resolution of their lymphoproliferative disorders.

One year later Trigg et al. [52] reported two more cases of PTLD treated with IFN-α. One was a 3-year-old girl who 6 weeks after a bone marrow transplant developed graft failure and received a second bone marrow transplantation after undergoing induction with anti-thymocyte globulin and cyclophosphamide. She began to have seizures within 2 weeks of the second transplant and was found to have PTLD involving the right cerebral hemisphere and the meninges. She received IFN-α with IVIg daily for 10 days. The dose was tapered off over a period of 4 months. The patient recovered

Table 3. Characteristics of patients with post-transplant lymphoproliferative disorders treated with IFN-α (modified with permission from O'Brien et al. [38])[a]

Patient	Age/Sex	Transplant	EBV	Site	Histology	Clonality	Other Rx	Outcome	Ref
1	36y/M	BMT	+, S/I	LN, lung	Polymorphic	+	Acy, IVIg	PTLD improved; died CMV pneu	[46]
2	30y/F	BMT	+, S/I	LN, lung	Polymorphic	–	Acy, IVIg	CR	[46]
3	3y/F	BMT				–		CR	[52]
4	6y/M	BMT				–		CR	[52]
5	4y/M	Liver	+, S/I	SI	Polymorphic	–	Surg, Acy, IVIg	CR	[25]
6	5y/F	Liver	+	LN, tonsils	Polymorphic	+	Acy, IVIg	CR	[49]
7	NA	Heart	+, S	LN	Immunoblastic	+	IVIg	CR	[24]
8	NA	Heart	+, S	SI	Immunoblastic	+	Surg, IVIg	CR	[24]
9	NA	Heart	–, S	Heart	Immunoblastic	+	Surg, IVIg, CT	PR, DWD	[24]
10	14y/M	Kidney	NA	LN, BM	Immunoblastic	+	Acy	PR, DWD	[31]
11	56y/F	Heart	+, S/I	LN, SI	Polymorphic	+	Acy	DWD	[31]
12	14y/F	Liver	+, S/I	LN, CNS, LI, tongue	Polymorphic	+	Acy, IVIg, CT, RT	CR	[31]
13	46y/F	Kidney	NA	ELR	Polymorphic	+	Acy	CR	[31]
14	6y/M	Heart/ Lung	+	Lung	Polymorphic	+		PR	[31]
15	11y/M	Lung	+, S/I	Lung	Polymorphic	NA	Acy	CR	[16]
16	65y/F	Kidney	+, S/I	LN	Immunoblastic	+	Acy, IVIg	CR	[38]
17	10m/M	Heart	+, S	SI	NA	NA	Acy	CR	
18	17y/F	Lung	+, S	Lung	Polymorphic	–	Gan, Cytogam	DWD	
19	15y/F	None	+, S	Trachea, Thy, NP	NA	–	NA	CR	[46]
20	17y/F	None	+, S	Liver	NA	–	NA	CR	[46]
21	12y/M	None	+, S	Liver, lung	NA	+	CT, steroids	CR	[46]

Patients 1–16 have been previously reported. Pateints 17 and 18 are unreported cases from Children's Hospital of Pittsburgh. Patients 19–21 are immunocompromised patients, but not transplant recipients. *EBV*, Epstein-Barr virus; *S*, serology; *I*, hybridization; *LN*, lymph nodes; *Acy*, acyclovir; *IVIg*, intravenous immunoglobulin; *DWD*, died with disease; *CR*, complete remission; *SI*, small intestine; *Surg*, surgical resection; *NA*, not available; *BM*, bone marrow; *P3*, partial remission; *CNS*, central nervous system; *CT*, chemotherapy; *LI*, large intestine; *RT*, radiation therapy; *ELR*, extralymphoreticular system; *Gan*, gancyclovir; *NP*, nasopharyngeal; *Cytogam*, CMV hyperimmune globulin; *y*, years

cerebral function and had no evidence of recurrent EBV infection. The second case was that of a 6-year-old boy who received a bone marrow transplant secondary to leukemia. Two months after the transplant he was diagnosed with PTLD and was started on IFN-α and IVIg for a 10-day course. He had rapid resolution of his symptoms and signs and the IFN-α was tapered off over a 4 month period.

Taguchi et al. [49] described a case of a 5-year-old girl who had received a liver transplant 3 years earlier because of α_1- antitrypsin deficiency. She presented with pharyngitis, adenopathy and fever. Tonsillectomy was performed and the specimen demonstrated PTLD. She improved with acyclovir and remained asymptomatic for 9

months; then redeveloped fever and lymphadenopathy. A cervical node biopsy confirmed the diagnosis of PTLD and she was again treated with acyclovir, but this time with a poor response. IFN-α and IVIg were initiated and her symptoms improved dramatically. One month following treatment she was diagnosed with biopsy-proven rejection. She improved with an increase in immunosuppression and did not have a recurrence of her PTLD. The authors found no CTL activity in this patient prior to therapy with IFN-α. After cyclosporine was discontinued and IFN-α was started, CTL activity returned.

Another small series of cases previously reported in the literature involved three heart transplant recipients [24], all following an immunosuppression regimen of cyclosporine, azathioprine and steroids. The first patient developed a surrenal mass, and the serology was positive for EBV. Within a week of beginning IFN-α and IVIg, a marked clinical response was noted. After 1 year of therapy with IFN-α and IVIg the mass had totally disappeared and treatment was discontinued 3 months later. The second patient presented with an ileal mass and, because of bowel obstruction, had the mass surgically removed. Therapy with IFN-α and IVIg was then started and the patient has remained in remission. The third patient was diagnosed with an intracardiac mass and a partial resection was performed. The patient's EBV serology was negative, but the histology revealed an immunoblastic lymphoma. Therapy with IFN-α and IVIg was instituted. The patient was disease free for 3 months and then suffered a local relapse and died. Levels of serum β-2 microglobulin, IFN-γ, G-CSF, sIL-2R, IL-10 and sCD23 were followed. In the first two patients IL-10 was elevated at the time of diagnosis and decreased with IFN-α therapy. The other markers were initially elevated and decreased with therapy. The third patient, whose serology was negative for EBV, never had a marked increase in the cytokine concentration.

Morrison et al. [31] reviewed the clinical course of 26 patients who developed PTLD. One patient received IFN-α as primary therapy. He achieved partial remission and was still alive 12 months after diagnosis. Four other patients received IFN-α after having received other treatments or in conjunction with other modes of treatment. Three of these received acyclovir as primary therapy and two achieved partial remissions. One survived 7 months and the other was still alive when the paper was published (10 months after diagnosis). The fourth patient in this group received acyclovir and chemotherapy, in addition to IFN-α and achieved complete remission.

In 1996, Faro et al. [16] reported a case involving an 11-year-old boy who developed PTLD 7 weeks after receiving a double lung transplant. He was initially treated with acyclovir and a reduction in his immunosuppression, which consisted of tacrolimus, azathioprine and prednisone. Because he remained symptomatic, IFN-α was initiated (100,000 U/kg body weight). Four weeks later there was dramatic clinical, radiographic, and histological improvement. Semiquantitative measurements of cytokine mRNA in cells recovered from serial bronchoalveolar lavages (BALs) revealed high levels of IL-4 and IL-10 mRNA. These levels decreased significantly with IFN-α treatment.

In a review of their experience with PTLD in pediatric thoracic organ recipients, Boyle et al. [6] report that three patients received IFN-α. One was the 11-year-old boy just discussed in the previous paragraph. Of the other two children, one is alive and well and the other died of complications including PTLD and rejection for which the IFN had to be discontinued (personal communication).

The most recent report concerns that of a 65-year-old woman who presented with a supraclavicular mass after receiving a second renal transplant [38]. She was main-

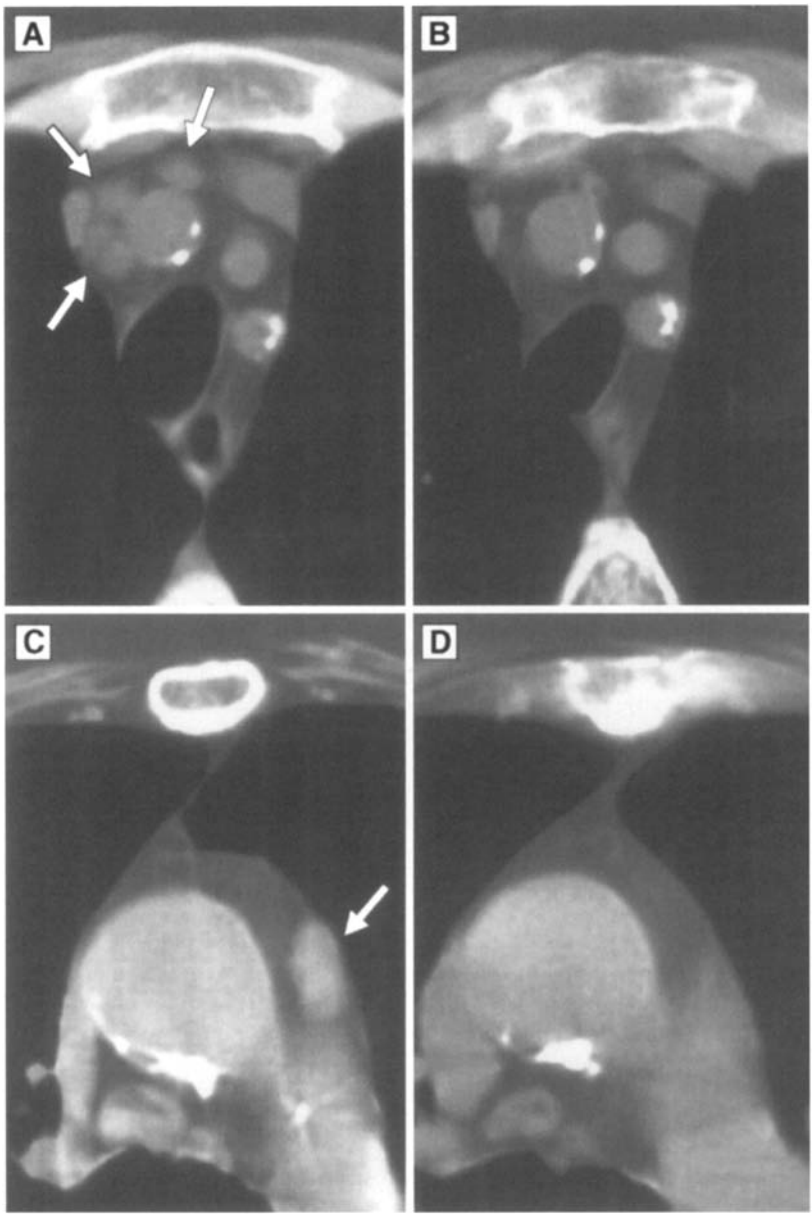

Fig. 1. Computed tomography (CT) scan of the chest at the time of diagnosis (**A**, **B**) and 4 months after therapy with IFN-α (**B**, **D**) Note that mediastinal and para-aortic lymph nodes (*arrows*) resolved completely after treatment (taken from O'Brien et al. [38] with permission)

tained on standard triple immunosuppression and had not received anti-lymphocyte therapy. Serology for EBV was positive. In addition, computed tomography (CT) scans demonstrated mediastinal, para-aortic, and right inguinal adenopathy. Because

of a lack of response to a decrease in immunosuppression and therapy with acyclovir and IVIg, treatment with IFN-α was instituted. After 20 days the adenopathy was noted to regress, and 4 months later there was complete resolution of the mediastinal and para-aortic adenopathy (Fig. 1).

Summary

EBV-transformation induces B lymphocytes to secrete high levels of human IL-10 [9]. Additionally, EBV contains a gene, BCRF1, that encodes for a protein that shares activity with human IL-10 in vitro. Thus, infection by EBV seems to promote a Th2 environment in the infected host. One may even hypothesize that EBV-derived IL-10 initiates a cascade of events that promotes a Th2 response and suppresses Th1 activity.

This is further confirmed by data that suggest elevated concentrations of IL-4, IL-10, and IgE in patients with PTLD [16, 29]. This implies an association between PTLD and an imbalance in the immunoregulatory system with either an excess suppression of Th1 cells and/or an up-regulation of Th2 cells. One could speculate that if the imbalance in the immunoregulatory system is corrected, the patient's own immune system could potentially defend itself against the virus. Clearly, this is the case in those immunocompromised patients with PTLD who respond to just a reduction in their immunosuppression. Unfortunately, this is only beneficial in approximately half of patients with PTLD [5]. Perhaps this is because patients often do not become entirely immunocompetent, either because all of their immunosuppression cannot be discontinued for fear of rejection or because once the above cascade is established the immune system is not capable of easily switching to the Th1 response necessary for combating the virus.

Theoretically, IFN-α, because of its anti-viral effect, its anti-neoplastic effect and/or possibly by its ability to promote a Th1 response, should be useful in the treatment of PTLD. IFN-α modulates the immune system by several mechanisms including: preventing B cells from producing immunoglobulins [7], reducing IL-6 receptor density [3, 46], and augmenting the inhibition of IL-4 by IL-12 [55]. In vitro studies document its effectiveness against EBV [17, 27, 30, 47].

Unfortunately, the available evidence as to its efficacy in vivo in patients with PTLD is very limited. At present, there are only 16 reported cases in the literature. There are also three cases of BLPD in immunocompromised patients that were all successfully treated with IFN-α [47] and the two cases alluded to earlier from Children's Hospital of Pittsburgh (personal communication). Although the numbers are small, the results are promising. Of the 21 patients with BLPD who received IFN-α, 15 achieved complete remission. Four others improved and 2 died from BLPD. One of the 4 that improved died 3 months later from a relapse. Thus, there was an overall mortality of 14% (3 of 21) in those who received therapy with IFN-α. This is a very heterogeneous group of patients, several of whom had also received additional therapies. Thus, it is impossible to draw definitive conclusions. However, the mortality rate in this group of patients, who had already failed therapy with a reduction in their immunosuppression, compares very favorably to the reported mortality rate of approximately 23–81% in patients with PTLD [5, 6, 31].

This data suggest that a large multi-centered prospective trial comparing IFN-α with and without IVIg to other treatment options (i.e., LAK cells) is warranted in those patients with EBV-positive PTLD who fail to respond to a reduction in their immunosuppression.

Acknowledgement. I would like to thank Jeffrey Brosco, M.D. and Gerard Boyle, M.D. for their invaluable assistance in writing this manuscript.

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