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B-cell lymphoma in a patient with complete interferon gamma receptor 1 deficiency

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Abstract

Immunosuppression-associated lymphoproliferative disorders can be related to primary as well as acquired immune disorders. Interferon gamma receptor (IFN-γR) deficiency is a rare primary immune disorder, characterized by increased susceptibility to mycobacterial infections. Here we report the first case of an Epstein Barr Virus (EBV) related B-cell lymphoma in a patient with complete IFN-γR1 deficiency.

The patient was a 20-year-old man with homozygous 22Cdel in *IFNGR1* resulting in complete absence of IFN-γR1 surface expression and complete lack of responsiveness to IFN-γ in vitro. He had disseminated refractory *Mycobacterium avium* complex and *Mycobacterium abscessus* infections. At age 18 he presented with new spiking fever and weight loss that was due to an EBV-positive B-cell non-Hodgkin lymphoma. Two years later he died of progressive lymphoma.

IFN-γ plays an important role in tumor protection and rejection. Patients with IFN-γR deficiencies and other immune deficits predisposing to mycobacterial disease seem to have an increased risk of malignancies, especially those related to viral infections. As more of these patients survive their early infections, cancer awareness and tumor surveillance may need to become a more routine part of management.

Keywords

B-cell lymphoma; interferon gamma receptor deficiency

Introduction

Susceptibility to mycobacteria is caused by a set of rare primary immunodeficiencies characterized by marked predisposition to infections with poorly pathogenic mycobacteria, such as nontuberculous mycobacteria (NTM) and Bacillus Calmette-Guérin (1). In addition,

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patients are susceptible to *Salmonella spp* (2), *Listeria monocytogenes* (3), dimorphic yeasts (4, 5), and some viruses (6-8). So far, mutations in eight different genes have been associated with mycobacterial susceptibility: interferon gamma receptors (IFNGR) 1 and 2, Signal Transducer and Activator of Transcription (STAT) 1, the p40 subunit of IL-12 and IL-23 (IL-12B), the β1 chain shared by the IL-12 and IL-23 receptor (IL-12RB1), nuclear factor-κB-essential modulator (NEMO), interferon response factor 8 (IRF-8) (9), GATA2 (10), CYBB (11) and ISG15 (12). Most of these defects are associated with some degree of impaired IFN-γ production or activity.

The relationship between immunosuppression and the development of lymphoproliferative disorders is well known. The so-called immunosuppression associated lymphoproliferative disorders (IALDs) are usually B-cell derived and Epstein Barr Virus (EBV) related, behave aggressively, and predominantly occur in extranodal sites (13). IALDs can be related to acquired immune disorders, such as infections with Human Immunodeficiency Virus (HIV) (14, 15), following organ or bone marrow transplantation (16), associated with the use of immunosuppressive therapy (17), or associated with primary immune disorders.

The incidence of lymphoproliferative disorders in patients with primary immune disorders ranges from 0.7-18% (13). Primary immunodeficiencies that are most commonly linked to an increased risk of IALD are severe combined immunodeficiency (SCID), X-linked hyper-IgM syndrome due to CD40L deficiency, common variable immune deficiency, X-linked agammaglobulinemia due to BTK deficiency, X-linked lymphoproliferative syndrome (XLP) due to SAP deficiency, autoimmune lymphoproliferative syndrome (ALPS) due to Fas and FasL deficiency, ataxia telangiectasia and Wiskott-Aldrich Syndrome (17). In addition, the occurrence of Hodgkin lymphoma has recently been reported in 2 patients with Chronic Granulomatous Disease (CGD) (18). So far, no lymphoproliferative disorders have been described in patients with syndromes predominantly predisposing to mycobacterial infections. To our knowledge, this is the first report of disseminated non-Hodgkin B-cell lymphoma in a patient with complete IFN-γR1 deficiency.

Case description

The patient was a 20-year-old Pakistani man born in Norway to consanguineous parents. He had complete IFNγ-R1 deficiency (homozygous 22Cdel in *IFNGR1*), resulting in complete absence of IFN-γR1 surface expression and complete lack of responsiveness to IFN-γ in vitro (19). His brother had died of disseminated NTM infection at age 6 years. The patient was started on antimycobacterial therapy at the age of 18 months when he first presented with disseminated *Mycobacterium avium* complex (MAC), after which he did reasonably well for several years. At age thirteen new submandibular and axillary lymphadenopathy yielded *M. abscessus* from tissue and blood; linezolid was added to azithromycin, ethambutol, rifabutin, moxifloxacin and ertapenem. After two years he had anorexia, weight loss, growth retardation and lymphadenopathy. *M. abscessus* was recovered from blood, liver, lung, lymph nodes and skin. Tigecycline was added to azithromycin, ethambutol, rifabutin and moxifloxacin and IFN-α 3 million units subcutaneously three times weekly was added to try to bypass the defect in IFN-γ signaling. He remained culture positive for *M. abscessus* despite several courses of aggressive intravenous antimycobacterial therapy. At age 18 he presented with new hectic fever and weight loss. CT chest and abdomen showed new nodular masses with necrosis in the right lung and liver (Figure 1A, B), biopsies of which showed focal necrosis with atypical CD20+ and MUM-1+ lymphoid cells (Figure 1C, 2A). EBV was detected by hybridization in atypical lymphoid cells and clonal rearrangement of the IgH locus was present, all consistent with an aggressive B-cell lymphoma (Figure 2B). The EBV blood load was elevated at 4800 EBV genomes/10^6 mononuclear cell equivalents and CMV was elevated at 5200-7300 genomes/ml of whole

blood. The patient declined chemotherapy in view of his persistent mycobacteremia, its likelihood of being exacerbated by chemotherapy, and his preference to return home. A short course of single agent rituximab was ineffective. He died at age 20 due to progressive disseminated non-Hodgkin lymphoma. An autopsy was not performed.

Discussion

IFN-γ is an immunomodulatory cytokine that plays important roles in both innate and adaptive immune responses (20). It is also crucial for cancer immunoediting, a process by which the immune response modulates the immunogenicity of tumors (21). IFN-γ is known to accentuate the immunogenicity of tumors increasing their likelihood of immune recognition and rejection. Multiple in vitro and murine cancer models have shown that mice lacking IFN-γR1 and/or STAT1 have higher rates of methylcholanthrene (MCA)-induced tumors, which occur more rapidly and more frequently than in wild type mice (21). Injection of recombinant IL-12 was associated with reduced metastases and tumor growth and even tumor regression in mice with established tumors, but abolished by administration of neutralizing anti-IFN-γ antibodies, illustrating the crucial role for IL-12 induced IFN-γ in tumor protection (22)]. Further, mice lacking IFN-γ are at risk for developing spontaneous lymphomas (23).

In humans, the occurrence and outcome of different types of malignancies have been associated with acquired mutations affecting IFN-γ signaling or production (24-26). In some reports, up to 25% of certain human tumor cell lines have complete and irreversible unresponsiveness to IFN-γ, allowing them to escape immune activation, evade IFN-γ-induced MHC display, and elude rejection (27). Proposed mechanisms underlying the protective role of IFN-γ in tumor prevention and response include direct anti-proliferative and pro-apoptotic effects, up-regulation of MHC class I, inhibition of tumor angiogenesis, and activation of innate and adaptive immune responses against tumor invasion (28, 29). The antiproliferative and pro-apoptotic effects of IFN-γ are thought to be mediated through STAT1-dependent upregulation of genes regulating cell cycle inhibition and cellular apoptosis, respectively (28). In addition, natural killer (NK) cells have been associated with anti-tumor activities through IFN-γ production as well as through direct cytolytic activity via perforin (30)] and TRAIL (31).

Two malignancies have been reported in patients with complete IFN-γR deficiency: one child with complete IFN-γR1 deficiency developed human herpesvirus-8 associated Kaposi sarcoma (7); another child with complete IFN-γR2 deficiency developed fatal disseminated squamous cell carcinoma (SCC) of the skin (32). In a retrospective study of 141 patients with IL-12RB1 deficiency, one case of esophageal carcinoma was recently described (1). Interestingly, the occurrence of both SCC of the skin as well as esophageal carcinoma have been associated with human papilloma virus (HPV) infections (32). Mutations in GATA2, a critical regulator of stem cell integrity, have recently been found in patients with a novel inherited immunodeficiency, characterized by an increased susceptibility to mycobacterial, fungal and viral (especially HPV) infections as well as to myelodysplasia and malignancy (10). Besides a clear predisposition to myelodysplasia and leukemia, HPV related cancers such as vulvar and cervical carcinoma as well as Bowen's disease of the vulva and EBV related leiomyosarcoma have been described in these patients.

Our patient's lymphoma was associated with high blood loads of EBV and CMV, and EBV positivity of the tumor was confirmed by additional staining. It seems likely that the occurrence of malignancies in patients with IFN-γ receptor deficiencies and other hereditary immunodeficiencies is linked to specific viral infections, especially those of the herpes

family. Patients with IFN-γ signaling disorders are at increased risk for developing severe viral infections, including herpes viruses (8).

This is the first report of non-Hodgkin lymphoma in a patient with IFN-γR1 deficiency. Since the first reports in 1996, almost 150 patients with either partial or complete IFN-γR1/2 deficiencies have been described (see (33) for an excellent review and (32, 34, 35) for a more recent update of total number of patients). In the US, the reported age-adjusted incidence rate of non-Hodgkin lymphoma is 1 per 5000 women and men per year (www.seer.cancer.gov). The fact that we have encountered one case of non-Hodgkin lymphoma out of a total of almost 150 patients with IFN-γR deficiencies (of which a substantial proportion is deceased), suggests that the incidence of non-Hodgkin lymphoma in patients with IFN-γR deficiencies may be higher than that of the general population, as would be predicted from the previous mouse and human studies. As more of these patients survive their early infections and enter the ages at which non-Hodgkin lymphoma is more common, tumor surveillance should become a more routine part of management. Because tumor prevention and rejection are so dependent on the integrity of immune cell IFN-γ signaling, bone marrow transplantation may correct both the infection predisposition and the propensity to lymphoid malignancies while leaving non-hematopoietic tissues still unable to respond to IFN-γ. Lymphoma is yet another risk for patients with predisposition to mycobacterial infections.

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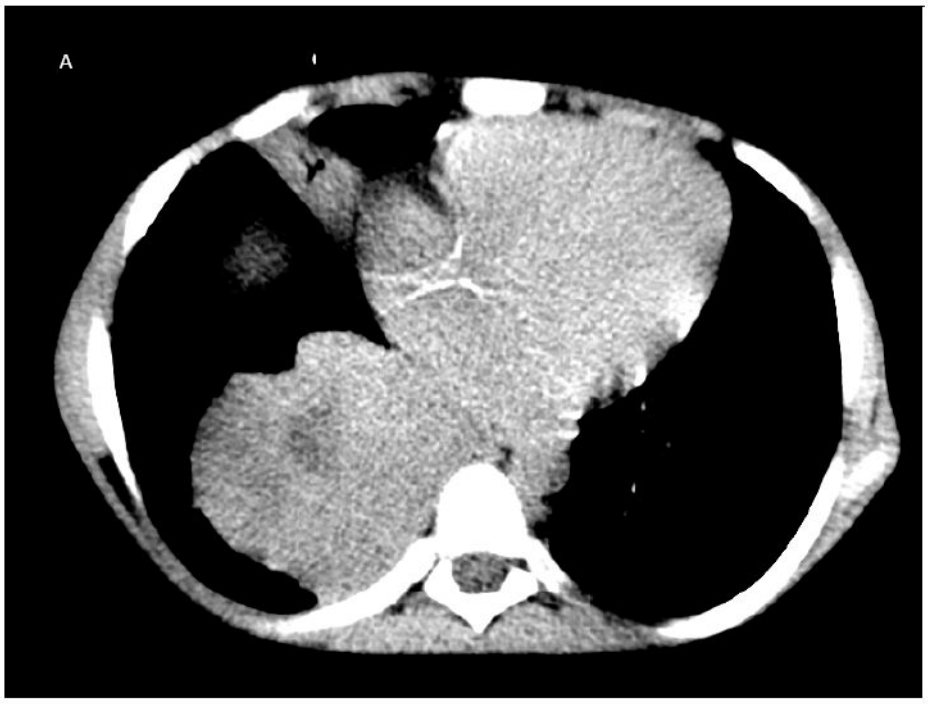

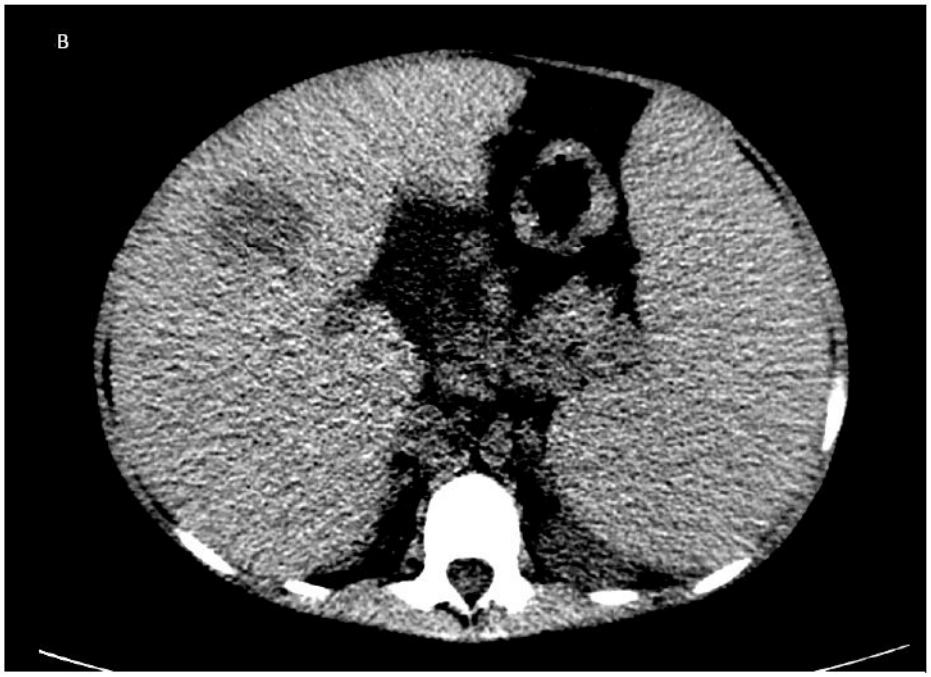

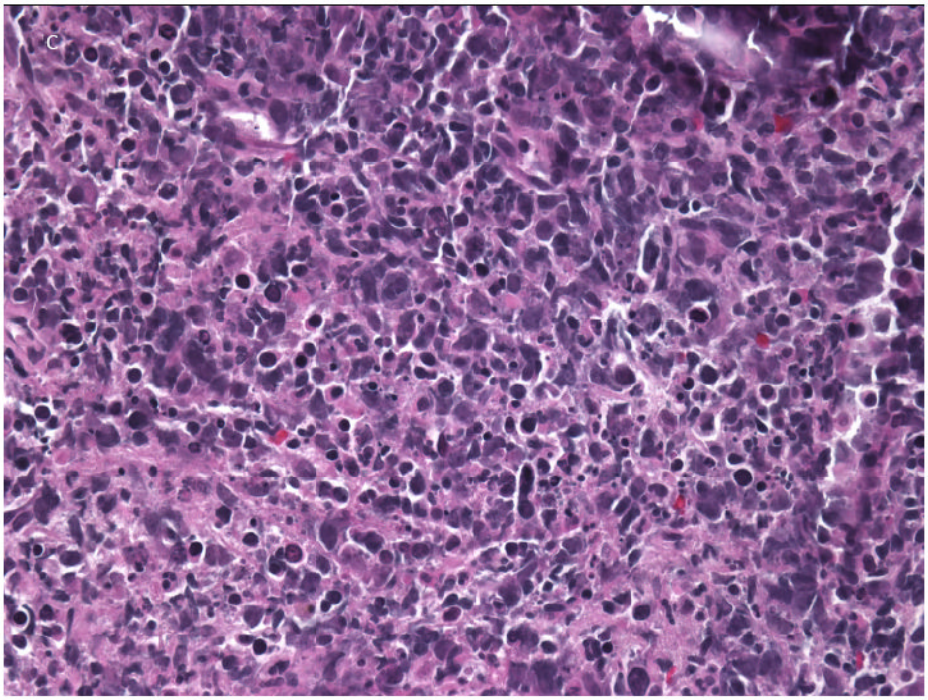

Figure 1.

A: Non-contrast chest CT showing extensive consolidation in the right lower lobe with central hypodensity consistent with necrosis. B: Non-contrast abdominal CT showing a large necrotic lesion in the anterior right lobe. C: Liver core biopsy from the necrotic area with pleomorphic lymphoid infiltrate composed of large cells with necrotic debris and frequent apoptotic bodies.

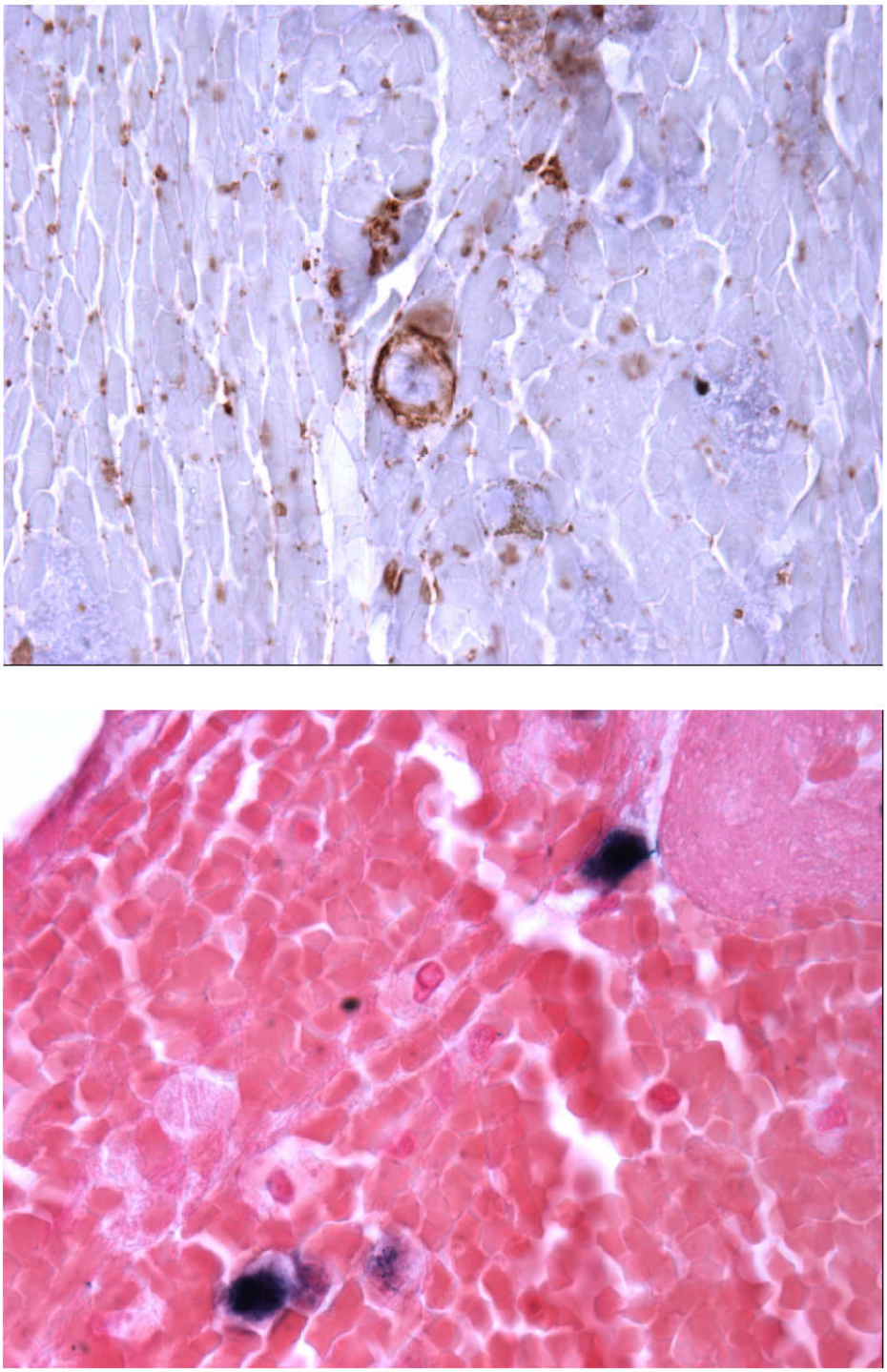

Figure 2.
Stains of the fine needle aspirate biopsy of the necrotic liver lesion. A. Immunohistochemistry for CD20+ cells, showing rare B cells. B. In situ hybridization for EBV, showing rare EBV+ cells consistent with EBV+ lymphoma. Images were taken using an Olympus Bx41 microscope, objective UPlanFI 40x/0.75 ∞/0.17, with an adaptor U-

TV0.5xC using a digital camera Q-imaging Micropublisher 5.0 RTV. The images were captured using “Q-Capture Version 3.1” and imported into Adobe Photoshop 7.0.