İst Tıp Fak Derg 2011; 74:3
J Ist Faculty Med 2011; 74:3
www.itfdergisi.com

DIFFUSE LARGE B-CELL LYMPHOMA AND LUPUS VULGARIS: A TALE OF TWO DISEASES

DİFFÜZ BÜYÜK B-HÜCRELİ LENFOMA VE LUPUS VULGARİS: İKİ HASTALIĞIN HİKAYESİ

Gökhan OKAN*, Güzin ÖZARMAĞAN**

ABSTRACT

Multi-drug resistant tuberculosis is problematic in immunocompromised individuals. In such patients, CD4 lymphocytopenia appears to correlate with the severity of the disease and with low interferon gamma production in response to infection with Mycobacterium tuberculosis. Treatment with interferon gamma may be a useful adjunct therapy in those patients. In this report, we describe a patient with idiopathic CD4 lymphocytopenia who presented with diffuse large B cell lymphoma after interferon gamma therapy for drug resistant tuberculosis. Gamma interferon treatment may be of benefit to patients with impaired cellular immune response. Before that therapy is initiated the clinicians should consider the patient's CD4 cell count considered carefully.

Key words: Idiopathic CD4 lymphocytopenia, ınterferon gamma, multi-drug-resistant tuberculosis, large b-cell lymphoma, Epstein-Barr virus

ÖZET

Bağışıklık sistemi zayıflamış hastalarda çok ilaca dirençli tüberküloz bir problemdir. Bu hastalarda CD4 lenfositopenisi hastalığın şiddeti ile ilişkilidir ve mycobacterium tuberculosis enfeksiyonuna yanıt olarak düşük gamma interferon üretiminden sorumludur. Bu hastalarda gamma interferon tedavisi faydalı bir yardımcı tedavi olabilir. Bu yazıda idiopatik CD4 lenfositopenisi olan bir hastada çok ilaca dirençli tüberküloz nedeniyle gamma interferon tedavisi sonrası diffüz büyük B hücreli lenfoma gelişmesi tanımlanmaktadır. Bağışıklık sistemi baskılanmış olan hastalarda gamma interferon tedavisi faydalı olabilir fakat bu tedaviye başlamadan önce klinisyenler hastanın CD4 hücre sayısına dikkat etmelidirler ve bu bilgi tedavi seçeneklerine karar verilmeden önce dikkatli bir şekilde düşünülmelidir.

Anahtar kelimeler: İdiopatik CD lenfositopenisi, interferon gamma, çok ilaca dirençli tüberküloz, büyük b hücreli lenfoma, Epstein Barr virüsü

INTRODUCTION

Multi-drug-resistant (MDR) tuberculosis is problematic in immunocompromised individuals (5). Patients with idiopathic CD4 T-lymphocytopenia(ICL) exhibit defective production of cytokines such as tumor necrosis factor alpha and interferon gamma. The administration of interferon gamma to such patients however can lead to an improvement in cellular immunity (11) that may potentiate the effects of anti-mycobacterial therapy.

We have previously reported on a patient with multidrug-resistant tuberculosis associated with ICL who also exhibited primary amenorrhea, mental retardation and a paracentric inversion of chromosome 14(12). Because of her progressive tuberculosis, treatment with interferon gamma was initiated. Six months after the discontinuation of that therapy, the patient was diagnosed as having diffuse large B-cell lymphoma.

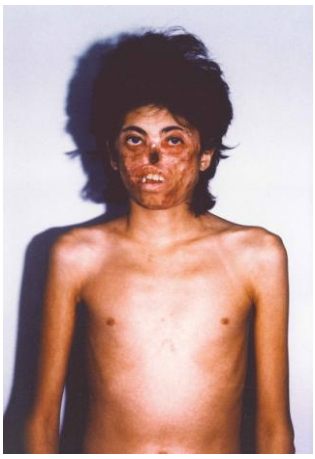
It is unclear whether that type of lymphoma is caused by ICL or by a chromosomal abnormality. In this report we describe the long-term follow-up of that individual.

Date received/Dergiye geldiği tarih: 11.07.2011 - Dergiye kabul edildiği tarih: 03.08.2011

* Medikal Park Bahçelivler Hastanesi, Dermatoloji Bölümü, İstanbul
(İletişim kurulacak yazar: gokhanokan8@hotmail.com)
** İstanbul Üniversitesi, İstanbul Tıp Fakültesi, Dermatoloji Anabilim Dalı, Çapa, İstanbul

CASE

A 19-year-old woman had been admitted to our dermatology department with endurated plaque on her nose. The results of a skin biopsy of the lesion revealed a granulomatous reaction. The diagnosis of cutaneous tuberculosis was based on the clinical and histopathologic findings. In this patient, who was born to consanguineous parents and was mentally retarted, external genitalia and secondary sexual characteristics were absent (Figure 1). Antituberculosis therapy both first line (isoniazid, ethambutol, rifampicin, pyrazinamide) and second line(ciprofloxacin, clarithromycine) had been started and had been found ineffective. Because the patient had failed to responsol to treatment, persistent lymphocytopenia (200 /mm³) and a ratio of less than 1.0 CD4/CD8, ICL had been diagnosed. She had also paracentric inversion of chromosome 14(46 xx, 14 q11-q32) and multiple chromosomal deletions. The disease progressed and new lesions developed (Figure 2). Six year after clinical diagnosis, polymerase chain reaction(PCR) search had revealed the presence of Mycobacterium tuberculosis DNA. Because she had not demonstrated a response to long courses of treatment, the decision to initiate therapy with interferon gamma was made. Before treatment with interferon gamma was begun, the patient's CD4+ T lymphocyte count was 50 mm³. She was treated with 50 μg/m^2, of subcutaneously administered interferon gamma 3 times per week for 5 months (Imukin, Boehringer Ingelheim) and received no other medications during that time although her condition was evaluated every 3 weeks. After that regimen, a partial improvement in her lesions was noted. During the course of therapy with interferon gamma, those lesions decreased in size and became less erythematous (Figure 3). Because of a moderate elevation of liver enzymes and the development of arthralgia and myalgia, interferon gamma therapy was discontinued after 5 months of treatment. Six months after the termination of that therapy, this patient began to cough and lose weight and she exhibited shortness of breath and hoarseness.



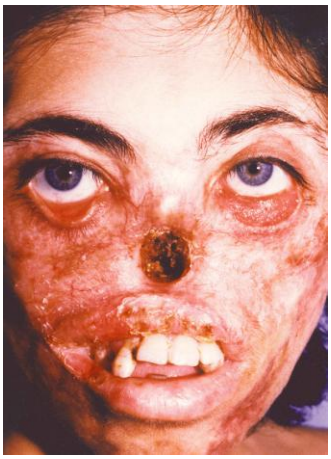
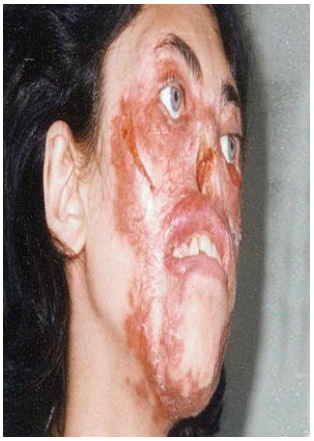


Figure 1 and Figure 2. Absence of secondary sexual characteristics & An erythematous ulcerated lesion on the face in a patient with ICD and cutaneous tuberculosis.



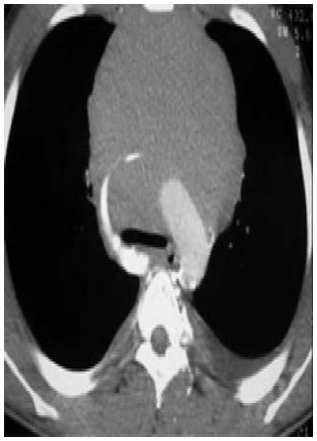


Figure 3 and Figure 4. Partial improvement after interferon gamma therapy & Computed tomography reveals a mediastinal mass in a patient with diffuse large B-cell lymphoma.

A physical examination revealed diffuse lymphadenopathy in the supraclavicular, axillary and cervical regions. The results of serologic tests showed a prior infection with Epstein-Barr virus and abdominal examination indicated hepatomegaly. A computed tomographic scan of the thorax showed enlarged mediastinal lymph nodes (Figure 4) and excisional biopsy of a lymph node specimen revealed dense lymphoid infiltrates that had abundant clear cytoplasm. Sclerotic areas were also noted. Those findings were consistent with diffuse large B-cell lymphoma. The patient's family refused treatment for this patient and she died 4 months after the diagnosis. The family also refused an autopsy.

DISCUSSION

Lupus vulgaris is a progressive form of tuberculosis that tends to occur in individuals with a variable degree of immune dysfunction. The diagnosis of cutaneous tuberculosis can be difficult, due to its resemblance to many other dermatological conditions. The diagnosis is based on clinical and histopathological findings. PCR has been shown to be better than that of microscopic examination and comparable with that of culture.

For patients in whom cutaneous tuberculosis remains a strong possibility, a therapeutic test of improvement after anti tuberculotic therapy has been approved as a diagnostic tool (1). increasing MDR-TB is a global problem. World Health Organisation guideliness for MDR-TB have been established for pulmonary tuberculosis but no recommendations are available for cutaneous tuberculotic. The reasons for this could be that very few cases of MDR-TB have been reported, the number of organisms present in the skin lesions is quite small and isolation of M. Tuberculosis on culture is low in cases of cutaneous tuberculosis. Cutaneous MDR-TB is defined as resistance to both isoniazid and rifampicin (13). More severe mycobacterial infections and MDR-TB are common in patients with ICL. Patients with ICL exhibit insufficient production of the proinflammatory mediators interferon gamma and tumor necrosis factor-alpha thus cytokine-based therapy is one of the last treatment options for patients with MDR-TB. Vaccination against *Mycobacterium vaccae* and the administration of interleukin 2 or interferon gamma have been promising in the treatment of ICL in small

preliminary studies (14). Holland and colleagues used interferon gamma in addition to antimycobacterial therapy to treat 4 patients with ICL who had a disseminated nontuberculous mycobacterial infection. Within 8 weeks of the initiation of interferon gamma therapy, those patients exhibited a clinical improvement (6). After interferon treatment our patient experienced a partial improvement and her lesions became smaller and less erythematous.

Treatment with interferon gamma causes many adverse effects. Most common of which are fatigue, arthralgia, myalgia, fever, nausea, vomiting, chest pain and the transient elevation of liver enzymes (10). Because of treatment-related adverse effects, therapy with interferon gamma was discontinued in our patient.

Diffuse large B-cell lymphoma is the most common type of lymphoma in adults and immunodeficiency is a significant risk factor for that disease (9). Holland and colleagues. reported on an ICL patient with non-Burkitt's large cell lymphoma that developed during interferon gamma therapy for a Mycobacterium avium infection (6). As soon as the lymphoma was diagnosed, gamma interferon treatment was discontinued and the patient was treated for lymphoma. These authors concluded that the patient's lymphoma may have been associated with the immunodeficiency that causes Epstein-Barr virus reactivation. Campbell and colleagues described an ICL patient with diffuse large B-cell lymphoma that developed several years after. The patient had also subclinical evidence of SLE. They concluded that immunosuppression resulting from the co-existence of ICL and probable autoimmune disease could contribute to the development of lymphoma (2). Mediastinal large B cell lymphoma is a subtype of diffuse large B-cell lymphoma that occurs primarily in young women who always present with a mediastinal mass (4). Mediastinal large B-cell lymphoma also develops in patients with human immunodeficiency virus and appears to occur in patients with a low CD4 T cell count (8). Cytogenetic abnormalities of chromosome 9,12 and xq have been identified in patients with that type of lymphoma (15) and rare cases of mediastinal B-cell lymphoma with t(14; 18) have also been described (7). Mediastinal large B cell lymphoma developed in our patient 6 months after the termination of treatment with gamma interferon. In patients with a healthy immune system, the proliferation of B cells infected with Epstein-Barr virus is prevented by cytotoxic T cells and a latent infection develops. In immunodeficient patients, infected B cells proliferate and B-cell lymphoma develops (3). The extent to which Epstein-Barr virus infection contributed to the development of lymphoma in our patient remains unclear.

Our case report shows that that clinicians must be aware of their patients' CD4 +T cell counts before interferon gamma therapy is initiated. In patients with MDR-TB, gamma interferon treatment is an option but the initiation of that therapy should be preceded by multiple evaluations of the CD4 T cell count to prevent reactivation of Epstein-Barr virus infection.

REFERENCES

1. Akoglu G, Karaduman A, Boztepe G, Ozkaya O, Sahin S, Erkin G, Kolemen F. A case of lupus vulgaris successfully treated with antituberculous therapy despite negative PCR and culture. Dermatology 2005; 211: 290-292.
2. Campbell JK, Prince HM, Juneja SK, Seymour JF, Slavin M. Diffuse large cell lymphoma and t(8; 22) (q24; q11) in a patient with idiopathic CD4+ T-lymphocytopenia. Leuk Lymphoma 2001; 41: 421-423.
3. Cohen JI. Epstein-Barr virus lymphoproliferative disease associated with acquired immunodeficiency. Medicine(Baltimore) 1991; 70: 137-160.
4. Coso D, Rey J, Bouabdallah R. Primary mediastinal B-cell lymphoma. [in French] Rev Pneumol Clin 2010; 66: 32-35.
5. Geffner L, Yokobori N, Basile J, Schierloh P, Balboa L, Romero MM, Ritacco V, Vescovo M, Gonzalez Montaner P, Lopez B, Barrera L, Aleman M, Abatte E, Sasiain MC, de la Barrera S. Patient with multidrug-resistant tuberculosis display impaired Th1 responses and enhanced regulatory T-cell levels in response to an outbreak of multidrug-resistant Mycobacterium tuberculosis M and Ra strains. Infect Immun. 2009; 77: 5025-5034.
6. Holland SM, Eisenstein EM, Kuhns DB, Turner ML, Fleisher TA, Strober W, Gallin JI. Treatment of refractory disseminated nontuberculous mycobacterial infection with interferon gamma: A preliminary report. New Engl J Med 1994; 330: 1348-1355.
7. Johnson PW, Davies AJ. Primary mediastinal B-cell lymphoma. Hematol Am Soc Hematol Educ Program 2008: 349-358 .
8. Kelemen K, Cao W, Peterson LC, Evens AM, Variakojis D. Primary mediastinal large B-cell lymphoma in HIV: Report of two cases. J Hematop 2009; 2: 45-49.
9. MacKenzie P, Kamili QU, Menter A, Cooper B. Lymphoma and immunosuppression: a report of a case associated with efalizumab therapy. Clin Lymphoma Myeloma Leuk. 2010; 10:14-16.
10. Miller CH, Maher SG, Young HA. Clinical use of Interferon-gamma. Ann N Y Acad Sci 2009; 1182: 69-79.
11. Netea MG, Brouwer AE, Hoogendoorn EH, Van der Meer JW, Koolen M, Verweij PE, Kullberg BJ. Two patients with cryptococcal menengitis and idioapthic CD4 lymphopenia: defective cytokine production and reversal by recombinant interferon-gamma therapy. Clin Infect Dis 2004; 39: 83-87.
12. Ozarmagan G, Ozgüroglu EZ, Maden MU, Ozturk S. Refractory ulcerative lupus vulgaris associated with CD4 lymphocytopenia, inversion of chromosome 14, primary amenorrhoea and mental retardation. Acta Derm Venereol 1997; 77: 309-310.
13. Ramesh V, Sen MK, Nair D, Singla R, Sengupta A. Cutaneous tuberculosis caused by multidrug-resistant tubercle bacilli: report of three cases. Int J Dermatol 2011 March; 50: 300-303.
14. Rivero-Lezcano OM. Cytokines as immunomodulators in tuberculosis therapy. Recent Pat Antiinfect Drug Discov 2008; 3: 168-176.
15. Scarpa A, Taruscio D, Scardoni M, Losi F, Paradisi S, Ennas MG, Rigaud G, Moore PS, Menestrina F. Nonrandom chromosomal imbalances in primary mediastinal B-cell lymphoma detected by arbitrarily primed PCR fingerprinting Genes Chromosomes Cancer 1999; 26: 203-209.