CASE REPORT

Adult Langerhans Cell Histiocytosis with Independently Relapsing Lung and Liver Lesions That was Successfully Treated with Etoposide

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Abstract

A 35-year-old man initially presented with cough and fever. Computed tomography (CT) revealed diffuse small cysts in the lung, and multiple nodules in the liver. Lung and liver biopsies revealed that pathology was consistent with Langerhans cell histiocytosis. Lung shadows increased despite cessation of smoking, whereas the liver involvement improved. After initiating treatment with prednisolone, the chest CT findings improved. However, the liver nodules started to increase while tapering prednisolone. Intravenous etoposide was started, and the liver nodules decreased markedly. The difference in the clinical course between the lung and liver lesions might have been the result of differences in the clonality of these two organs.

Key words: Langerhans cell histiocytosis, liver, lung, etoposide

Introduction

Langerhans cell histiocytosis (LCH) is a rare disorder of uncertain etiology, characterized by a wide clinical spectrum and varied behavior. Recent biological studies have shown that systemic LCH is a clonal proliferative disorder (1), and positive responses with several chemotherapeutic agents have been reported (2, 3). In contrast with systemic LCH, pulmonary LCH (PLCH) occurs almost exclusively in adult smokers. These patients often improve spontaneously or enter remission once smoking is stopped (4, 5). Molecular analysis has revealed that this disease is usually nonclonal, indicating that inflammatory processes are involved in the development of PLCH (4).

Here, we report the interesting clinical course of an adult patient with LCH who had lung and liver involvement. In this patient, lung and liver lesions were noted to relapse and remit independently. The liver lesions were refractory to corticosteroid therapy, but were successfully treated with intravenous etoposide. The different responses to the therapies indicate that there may have been a difference in clonality between the lung and liver lesions.

Case Report

An obese 35-year-old man (body mass index, 26.7 kg/m²) was admitted to Shinshu University Hospital in June 1998 with dry cough and high fever (38°C) (Fig. 1). The patient had a history of smoking 20 cigarettes/day for 20 years. Physical examination, including skin, lymph nodes, and chest auscultation yielded otherwise normal results. Levels of serum C-reactive protein (CRP; 9.48 mg/dl) and alanine aminotransferase (ALT; 81 IU/l) and erythrocyte sedimentation rate (ESR; 68 mm/h) were elevated. Pulmonary function testing revealed reduced carbon monoxide diffusion capacity (%DLco 66.9%). Chest computed tomography (CT) revealed a diffuse pattern of small cysts, located predominantly in the upper and middle lung lobes (Fig. 2). Abdominal CT showed multiple, well-defined round and oval nodules within the liver. On contrast enhancement, small nodules displayed rapid enhancement. Large nodules presented as well-circumscribed hypotenuating lesions with ring enhancement (Fig. 2). Magnetic resonance imaging (MRI) of

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the central nervous system and whole bone scintigraphy displayed no abnormalities. Based on radiographic findings and smoking history of the patient, PLCH was suspected. On pathological examination of thoracoscopic lung and liver biopsy specimens, granulomatous lesions displayed CD1 and S-100 protein-positive histiocytes with infiltration of eosinophils and fibrous lesions (Fig. 3, immunohistochemical staining for CD1 and S-100; not shown). A diagnosis of LCH was thus established.
Figure 4. Findings from chest and abdominal CT in August 1998, 2 months after diagnosis (2 months after smoking cessation). Diffuse nodular lung shadows that have increased in size and decreased liver involvement is evident.

Figure 5. Chest and abdominal CT findings in June 1999 during tapering of prednisolone (7.5 mg/day). Hepatic nodular shadows that increased in size and pulmonary cystic nodules that did not increase in size are evident.

Despite cessation of smoking, diffuse nodular lung shadows had increased in size at 2 months after diagnosis (Fig. 4), although liver involvement improved (Fig. 4). The patient was treated with prednisolone (35 mg/day) and chest CT findings improved. However, the patient developed high fever associated with leukocytosis (13,040/μl) and elevated CRP levels (2.94 mg/dl) 10 months later during tapering of prednisolone (7.5 mg/day). Hepatic nodular shadows increased in size (Fig. 5), but chest CT did not show recurrent pulmonary cystic nodules (Fig. 5). After fever developed, in association with the recurrence of the liver lesions, the patient resumed smoking (10 cigarettes/day). The patient was again treated with prednisolone 35 mg/day, but CT revealed no improvement in liver lesions, and his fever did not resolve.

At this point, the patient moved to our town and was referred to our hospital. Steroid pulse therapy (methylprednisolone sodium succinate 1 g/day for 3 days) was started followed by oral administration of prednisolone at 60 mg/day. His fever resolved, hepatic nodular shadowing improved, and CRP levels normalized. However, 10 months later, during the tapering of prednisolone (15 mg/day), the patient’s symptoms relapsed and developed high fever, leukocytosis (14,100/μl), elevated CRP levels (5.47 mg/dl), and an increase in the size of hepatic nodular shadows (Fig. 6). At the same time, lung CT showed further improvements in cystic nodular lung lesions. An increased dose of prednisolone to 40 mg/day did not show any efficacy. In September 2000, intravenous etoposide was started (200 mg/m² on 3 consecutive days) for 5 cycles, given at 3-week intervals. Since the use of etoposide is associated with an increased risk of developing therapy-related malignancy, informed consent was obtained from the patient before treatment. After finishing this treatment course, liver lesions were markedly decreased in size and number, and CRP levels normalized. At the time of this writing, the patient is no longer taking prednisolone, and no episodes of inflammatory reaction have been noted during the 5 years of follow-up after etoposide treatment (Fig. 7).
Figure 7. Findings from chest and abdominal CT in 2006, five years after the treatment with etoposide. The liver lesions have markedly decreased in size and number.

Discussion

Although the present case had lung involvement, several clinical findings were quite unique and distinguish this case from the PLCH that is generally seen in adult smokers. First, despite smoking cessation, diffuse nodular lung shadows increased in size, and the resumption of smoking did not affect disease activity. Second, the lung and liver lesions relapsed and remitted independently; at no time did both regions have simultaneous relapses or remissions. Third, with respect to the liver lesions, although prednisolone was initially partially effective, relapses occurred during tapering of high-dose prednisolone; finally, treatment with etoposide was effective. These findings differentiate this case from the usual case of PLCH seen in adult smokers, in which inflammatory processes are involved in disease development (4). A difference in clonality may have existed between the lung and liver lesions; clonal progression might have been more involved in the development of the liver lesions than in the lung lesions. To our knowledge, this is the first case report of adult LCH in which the two organs that were involved relapsed and remitted independently. This is also the first case report of adult LCH in which etoposide was effective for the treatment of liver lesions.

Liver involvement in adult LCH is relatively rare (6-8). Nagai et al reported 1 case of adult LCH with liver involvement (8) and reviewed 5 previously reported adult cases (9-13). Interestingly, in their case, radiographic findings of both the lungs and the liver displayed marked improvements after smoking cessation; the case was described as “PLCH with liver involvement”. In contrast, in the present case, despite smoking cessation, the diffuse nodular lung shadows an increase in size. These findings indicate that our case is distinct from the case presented by Nagai et al, and that in our case smoking was not the stimulus for disease development.

Although the treatment of LCH in children is well established (14), the treatment of LCH in adults remains controversial. In the present case, increased prednisolone (40 mg/day) was not effective after the second recurrence of liver lesions; thus, several agents, including immunosuppressants or cytotoxic agents, were considered. Eventually, etoposide was chosen for two reasons. First, smoking was not associated with the development of lung or liver lesions, indicating that this case is distinct from PLCH and that clonal progression may have been involved, particularly in the development of the liver lesions. Second, the efficacy of etoposide has been reported in some adult cases with relapsing LCH (2, 3). Our patient’s response suggests that intravenous etoposide is useful for treating corticosteroid-resistant LCH. During 5 years of follow-up, the present case has had no inflammatory reaction episodes after etoposide treatment. However, since the use of etoposide is associated with an increased risk of developing therapy-related malignancy, careful long-term follow-up is required.

In summary, we treated a case of adult LCH that had an interesting clinical course. The lung and liver lesions relapsed and remitted independently. Finally, etoposide was effective for treating the liver lesions. A detailed molecular analysis will provide the mechanistic insight for the pathogenesis of the different clinical courses and the different responses to the therapies of the two organs.

References


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