

Successful Cyclophosphamide Therapy in Recurrent Eosinophilic Colitis Associated with Hypereosinophilic Syndrome

Ju-Hee Lee, Jin Woo Lee, Cheol Soon Jang, Eun Sang Kwon, Hyo Young Min, Seok Jeong, Kye Sook Kwon, Don Haeng Lee, Hyeon Geun Cho, Pum-Soo Kim, Hyung Gil Kim, Yong Woon Shin, and Young Soo Kim

Department of Internal Medicine, Inha University College of Medicine, Incheon, Korea.

Eosinophilic colitis is a relatively rare complication of hypereosinophilic syndrome which is characterized by abdominal pain and bloody diarrhea and is usually treated with steroids and hydroxyurea. However, no standard regimen exists in cases of intractable disease despite several treatment attempts with Interferon- α , cyclosporin, etoposide, and vincristine, etc. We here report a case of a 43-year-old woman with recurrent eosinophilic colitis as a complication of hypereosinophilic syndrome who was successfully treated with cyclophosphamide.

Key Words: Hypereosinophilic syndrome, eosinophilic colitis, cyclophosphamide

INTRODUCTION

Hypereosinophilic syndrome (HES) is a systemic disease of unknown cause characterized by persistent peripheral eosinophilia and eosinophilic infiltration of tissue, resulting in severe organ dysfunction. Although any organ system may be involved, the heart, nervous system, lungs and skin are most frequently involved.^{1,2} Gastrointestinal tract involvement can accompany HES,^{3,4} but the association of severe eosinophilic colitis with this syndrome has been very rarely described. Generally, eosinophilic colitis is treated by a combination therapy of steroids and hydroxyurea.^{5,6}

However, for the patient presented here, this regimen was not effective after recurrence. Cyclophosphamide is a chemotherapeutic agent. Although other chemotherapeutic agents, such as Interferon- α ,⁷ cyclosporin,⁸ etoposide,^{9,10} and vincristine,¹¹ etc., have been frequently used with success, cyclophosphamide has not been reported to be effective in HES. But in other eosinophilic proliferative disease, such as the Churg-Strauss syndrome, this drug has been used successfully.^{12,13} In the following, we describe a case of recurrent eosinophilic colitis with HES which was successfully treated with steroids, hydroxyurea and cyclophosphamide.

CASE REPORT

A 43-year-old housewife was referred to our hospital for the evaluation of persistent eosinophilia, abdominal pain and bloody diarrhea in April 1998. Over a 6 year period previously, she had been recurrently admitted to multiple local hospitals due to abdominal pain with watery diarrhea and had been treated conservatively. She didn't have any pet or history of any previous illnesses including allergy, asthma and even insect bite.

On admission, her blood pressure was 110/70 mmHg, pulse rate 80/minute, respiratory rate 16/minute and body temperature 37.3°C. On physical examination, she appeared chronically ill. There were many pruritic erythematous papules on both the arms and the legs. Her other physical

Received April 25, 2001

Accepted October 12, 2001

Reprint address: requests to Dr. Pum-Soo Kim, Department of Internal Medicine, Inha University College of Medicine, Incheon, 400-103, Korea. Tel: 82-32-890-2548, Fax: 82-32-890-2549, E-mail: tyecos@inha.com

findings were unremarkable. Laboratory findings showed a hemoglobin concentration of 9.9 g/dL, a leukocyte count of 42,400/mm³ (eosinophil 15,688/mm³) and a platelet count of 458,000/mm³. A peripheral blood smear revealed eosinophilia with an increased number of immature leukocytes (shift to left). Further biochemical studies revealed; glucose 95 mg/dL, BUN 7 mg/dL, creatinine 0.8 mg/dL, protein 6.7 g/dL, albumin 2.8 g/dL, AST 45 IU/L, ALT 15 IU/L and LDH 436 IU/L. Stool examination was 2+ for occult blood. There was no evidence of parasites or ova in the feces. The skin tests for *Paragonimus westermani*, *Clonorchis sinensis*, sparganosis, cysticercosis and common ubiquitous antigens were all negative. She also had an elevated level of IgE over 1000 IU/ml. The results of thyroid function test, rheumatoid factor and Widal test were all within normal limits. Furthermore, the results of chest X-ray, abdominal ultrasonography, transthoracic echocardiography and small bowel series were also all non-specific. Upper gastrointestinal endoscopy showed multiple active ulcers on the antrum and the body. Colonoscopy (Fig. 1) revealed widespread inflammation with multiple aphthoid ulcers, contact bleeding and mucinous discharge throughout the entire colon. For pathologic diagnosis, biopsies were taken from multiple organs. The skin biopsy (Fig. 2) exhibited many lymphoplasma cells and eosinophils in the perivascular space. Bone marrow (Fig. 3) revealed a 60% ratio of mild hypercellularity and the M:E ratio was 13:1. There was an increased proportion of myeloid cells, especially mature eosinophils. On gastric biopsy, chronic active gastritis was evident on the antrum without *Helicobacter pylori*. Finally, colonic biopsy (Fig. 4) demonstrated eosinophilic infiltration in the intact crypt architecture and multiple small vascular thrombosis with ischemia and increased fibrosis.

From these observations, a diagnosis of HES with eosinophilic colitis was made and therapy began with prednisone, starting at a dose of 60 mg/day. After one week 1 g/day of hydroxyurea was added to the therapy. On this medication, all symptoms quickly subsided and she was discharged with a maintenance dose of prednisone and hydroxyurea (10 mg/day and 1 g/day, respectively).

However, in May 1999 she presented again with recurrent severe abdominal pain, bloody diarrhea and an increased peripheral eosinophil count of 9,856/mm³. Five cycles of cyclophosphamide chemotherapy were begun at a dose of 500 mg per month (total dosage of 2,500 mg over the 5 months), and after this period the therapy reverted to a maintenance dose of steroids and hydroxyurea. After an initial paradoxical increase of eosinophil, a gradual reduction in the eosinophil count was observed (Fig. 5). At the time of writing, the patient continues to do well and maintains a normal of eosinophil count in peripheral blood without significant complication.

DISCUSSION

Hypereosinophilic syndrome is characterized by a sustained overproduction of mature eosinophils and a toxicity to specific organs. There are several diagnostic criteria for the evaluation of this syndrome. Firstly, the patient must sustain a blood eosinophilia of greater than 1,500/mm³ for longer than 6 months. Secondly, other apparent etiologies of eosinophilia must be absent, including parasitic infections and allergic disease. Thirdly, the patient must exhibit signs and symptoms of organ involvement.¹ The main clinical complications of HES are endomyocardial disease, skin lesions, thromboembolism, gastrointestinal symptoms, cerebral lesions, splenomegaly and respiratory disease.^{2,3} Diarrhea is reported in over one fifth of patients with HES and colonic infiltrations of eosinophils are occasionally described.⁴ However, severe eosinophilic colitis is not yet frequently reported.¹⁴

Eosinophilic infiltration of the gastrointestinal tract occurs in many conditions including eosinophilic gastroenteritis, ulcerative colitis, allergic granulomatosis with angiitis (Churg-Strauss syndrome), helminthic disease, lymphoma and gastric cancer.^{15,16} When present as a complication of HES, the common symptoms of eosinophilic colitis are bloody diarrhea and abdominal pain. Digestive endoscopy examination typically reveals widespread mucosal ulcerations and a small intestine biopsy specimen shows pleomorphic eosinophilic infiltrates (10 - 20%) without granulo-



Fig. 1. Colonoscopy reveals multiple aphthoid ulcers.

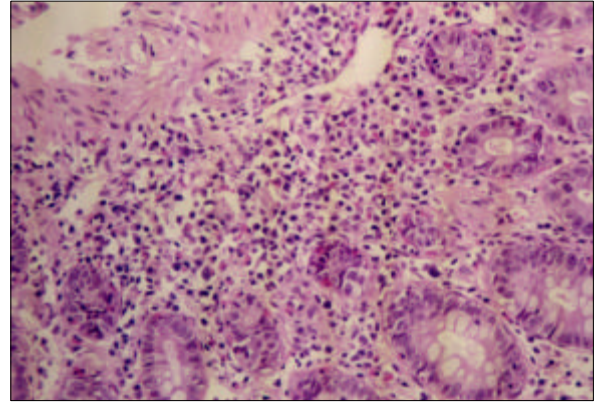


Fig. 4. Intact intestinal crypt architecture can be seen but widespread villous atrophy is also apparent. ($\times 200$ H & E stain)

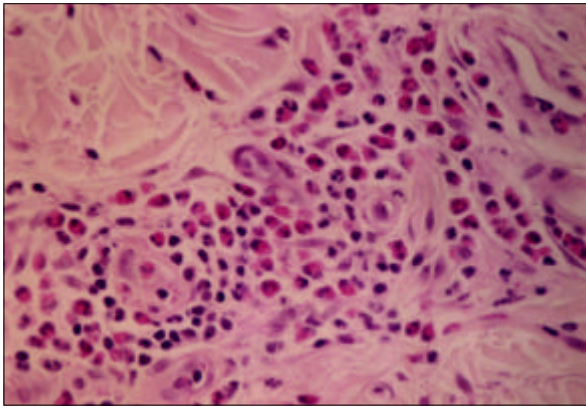


Fig. 2. Skin biopsy confirms perivascular mixed cell infiltration composed of lymphoplasmic cells and eosinophils. ($\times 400$ H & E stain)

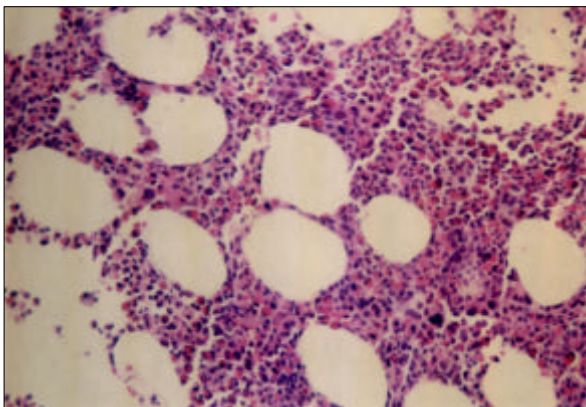


Fig. 3. Bone marrow examination shows hypercellular marrow with myeloid cell dominance, especially mature eosinophils. Reticulin fibrosis is mild. ($\times 200$ H & E stain)

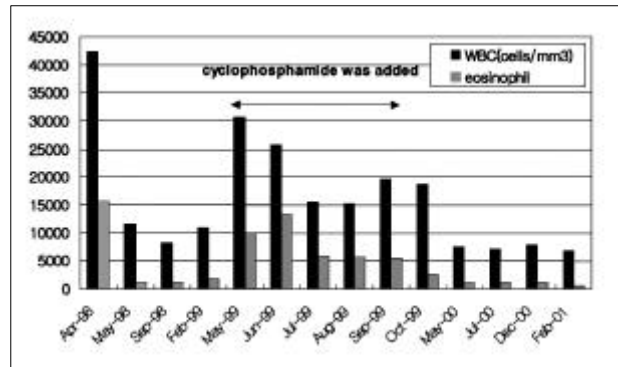


Fig. 5. Time courses of WBC and eosinophil counts.

ma and subtotal villous atrophy.¹⁶

Our patient presented with abdominal pain, bloody diarrhea and severe prolonged eosinophilia. There was no evidence of any other causes of eosinophilia. Colonic biopsies obtained during the episodes of colitis showed widespread mucosal ulceration, predominantly with eosinophils, but there was no evidence of granuloma formation. After the diagnosis of HES with eosinophilic colitis, steroids and hydroxyurea were initially prescribed but although this therapy was continued at a maintenance level, it resulted in recurrence after 12 months. Therefore, at recurrence we prescribed cyclophosphamide instead of the previous two drugs. Cyclophosphamide is a chemotherapeutic agent transformed primarily in the liver to active metabolites which interfere with the growth of rapidly proliferating cells by blocking the cross-linking of DNA. Cyclophospha-

mide has not been reported to be effective in the treatment of HES, although it has been used successfully in other eosinophilic proliferative disease, such as the Churg-Strauss syndrome.^{12,13}

To conclude, we prescribed cyclophosphamide for a case of intractable eosinophilic colitis, which had recurred in spite of an initial treatment consisting of steroids and hydroxyurea. As a result of using cyclophosphamide, remission of eosinophilia and the associated symptoms was successfully achieved and no serious complications have been found so far.

REFERENCES

1. Spry CJ. The hypereosinophilic syndrome: clinical features, laboratory findings and treatment. *Allergy* 1982;37:539-51.
2. Hardy WR, Anderson RE. The hypereosinophilic syndromes. *Ann Intern Med* 1968;68:1220-9.
3. Cello JP. Eosinophilic gastroenteritis - A complex disease entity. *Am J Med* 1979; 67:1097-104.
4. Fauci AS, Harley JB, Roberts WC, Ferrans VJ, Gralnick HR, Bjornson BH. NIH conference. The idiopathic hypereosinophilic syndrome. Clinical, pathophysiologic, and therapeutic considerations. *Ann Intern Med* 1982;97:78-92.
5. Parrillo JE, Fauci AS, Wolff SM. Therapy of the hypereosinophilic syndrome. *Ann Intern Med* 1978;89:167-72.
6. Marshall GM, White L. Effective therapy for a severe case of the idiopathic hypereosinophilic syndrome. *Am J Pediatr Hematol Oncol* 1989;11:178-83.
7. Papo T, Piette JC, Hermine O. Treatment of the hypereosinophilic syndrome with interferon-alpha. *Ann Intern Med* 1995;123:155-6.
8. Akiyama Y, Shimizu A, Kimura A, Onodera R, Minatani M, Horikoshi K, et al. Successful treatment of hypereosinophilic syndrome with cyclosporin and steroids. *Nihon Kyobu Shikkan Gakkai Zasshi* 1997;35:541-5.
9. Andries JS, Lammert HE & Elisabeth GE. Successful long-term control of idiopathic hypereosinophilic syndrome with etoposide. *Cancer* 1991;67:2826-7.
10. Smit AJ, van Essen LH, de Vries EG. Successful long-term control of idiopathic hypereosinophilic syndrome with etoposide. *Cancer* 1991;67:2826-7.
11. Van Slyck EJ, Adamson TC 3rd. Acute hypereosinophilic syndrome. Successful treatment with vincristine, cytarabine, and prednisone. *JAMA* 1979;242:175-6.
12. Ottolenghi A, Barnett HD. The effect of drugs on the eosinophilic leukocyte population of rat tissues. II. Cyclophosphamide. *J Pharmacol Exp Ther* 1974;189:312-6.
13. Guillevin L, Cohen P, Gayraud M, Lhote F, Jarrousse B, Casassus P. Churg-Strauss syndrome. Clinical study and long-term follow-up of 96 patients. *Medicine (Baltimore)* 1999;78:26-37.
14. Jung HK, Jung SA, Lee HC, Yi SY. A case of eosinophilic colitis as a complication of the hypereosinophilic syndrome. *Korean J Gastrointest Endosc* 1998;18:417-25.
15. Suen KC, Burton JD. The spectrum of eosinophilic infiltration of the gastrointestinal tract and its relationship to other disorders of angitis and granulomatosis. *Hum Pathol* 1979;10:31-43.
16. Shah AM, Joglekar M. Eosinophilic colitis as a complication of the hypereosinophilic syndrome. *Postgrad Med J* 1987;63:485-7.