CASE REPORTS OF THE UNIVERSITY OF PUERTO RICO
SCHOOL OF MEDICINE HOSPITALS

Crohn's Disease Associated to Chordoma: a Case Report

WILFREDO E. DE JESÚS-MONGE, MD*; ESTHER A. TORRES, MD*; VIRGEN M. BÁEZ, MD*; ORLANDO DE JESÚS, MD†; LUMARIE RIVERA, MD‡; CARMEN GONZÁLEZ-KEELAN, MD‡

Crohn's disease is an inflammatory bowel disease characterized by remissions and exacerbations. Immunosuppressants are frequently used to induce and maintain remission in these patients. The use of the immunomodulator azathioprine has been associated to malignancies. Chordomas are rare, locally aggressive tumors arising from remnants of the notochord. A specific trigger for this tumor has not been identified and association to any medication has not been reported. The purpose of this report is to present the first case reported in the literature of Crohn's disease associated to a chordoma. The patient to be presented was on azathioprine therapy, among other medications. A review of literature revealed that Crohn's disease and chordoma have abnormalities in chromosomes 1 and 10. Inflammatory bowel disease and chordoma also have abnormalities in chromosomal regions 1p, 3p, and 7q. Despite these findings, a direct genetic relationship between these diseases is speculative.

Key words: Crohn's disease, Chordoma, IBD, Azathioprine, Tumor, Genetics.

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) of unknown etiology affecting any portion of the gastrointestinal tract. One or more bowel segments may be affected, separated by intervening unaffected areas. The inflammatory bowel diseases, CD and ulcerative colitis, are more prevalent in industrialized countries. CD has peak incidences between ages 15 to 30 years and 60 to 80 years and females are affected slightly more often than males. The disease usually begins with intermittent attacks of mild diarrhea, fever, and abdominal pain.

Complications may arise from strictures or fistulas to other loops of bowel, perianal skin, urinary bladder, or vagina. A higher risk of gastrointestinal cancer has been reported after many years of disease. Medications used in the treatment of CD include aminosalicylates, corticosteroids, antibiotics, immunomodulators, and anti-tumor necrosis factor therapies (1). The immunomodulator azathioprine is a pro-drug that is converted to 6-mercaptopurine, which is later metabolized to 6-thioinosinic acid, the active metabolite that is incorporated into developing deoxyribonucleic acid strands. Treatment for 3 to 6 months with azathioprine or 6-mercaptopurine for IBD is frequently needed before a therapeutic response is evidenced. These drugs have been shown to be effective in induction and maintenance of remission in CD (2) and prevention or delay of postsurgical recurrence (1). Azathioprine (2) and its metabolite 6-mercaptopurine (1) have been associated to the development of malignancies (1). Chordoma is an aggressive tumor that arises from remnants of the notochord (3-4). One-third of all chordomas occur in the skull base and the clivus (3-4). The most commonly associated symptoms are headache and visual disturbances (3). The vital structures adjacent to a chordoma make a complete surgical resection difficult. The tumor expands and destroys bone. It has a high local recurrence tendency but low distant metastasis propensity. Microscopically, the tumor cells are arranged in lobules and delimited by fibrovascular septae (3). The cytoplasm is granular and eosinophilic (3). Physaliferous cells are large and vacuolated, with bubble-containing cytoplasm.

We present the case of a 27-year-old female with CD receiving azathioprine who developed a chordoma. To our knowledge, this is the first case of CD associated to a chordoma reported in the literature.

From the Departments of *Medicine, †Surgery (Neurosurgery Section), and ‡Pathology, Medical Sciences Campus, University of Puerto Rico, San Juan, Puerto Rico.

Address for correspondence: Esther A. Torres, MD, Chair and Professor, Department of Medicine, Room A-838, Medical Sciences Campus, University of Puerto Rico, P O Box 365067, San Juan, PR 00936-5067. Telephone: (787) 751-6034. Fax: (787) 754-1739. E-mail: eatorres@rcm.upr.edu.

Case Report

A 27-year-old female with a nine-year history of CD was found to have a calcification projecting above the dorsum sella and extending posterior to the clivus in a skull x-ray for evaluation of head trauma after a motor vehicle accident. The patient had a diagnosis of CD with perianal, rectal, colonic, and distal ileum involvement, chronically active. She had frequent episodes of diarrhea and abdominal pain, was underweight and had a symptomatic hypochromic microcytic anemia poorly responsive to iron replacement therapy, requiring red blood cell transfusions periodically. The patient had been treated with aminosalycilates (mesalamine, sulfasalazine, and olsalazine), metronidazole, intravenous and oral corticosteroids and azathioprine for the last five years. She had multiple hospitalizations due to CD exacerbations and erratic medication compliance. A rectal stricture required dilatation in the past. She did not have toxic habits or known allergies. Her family history was negative for IBD and colorectal carcinoma.

The patient referred history of headache, blurred vision, and dizziness for two years, but ophthalmologic evaluation was negative. Magnetic resonance imaging (MRI) of the brain was performed for evaluation of the abnormal skull x-ray series. An irregular and heterogenous lesion associated with bony expansion above and posterior to the clivus encroaching upon the sella turcica was demonstrated (Figure 1). The pituitary gland and

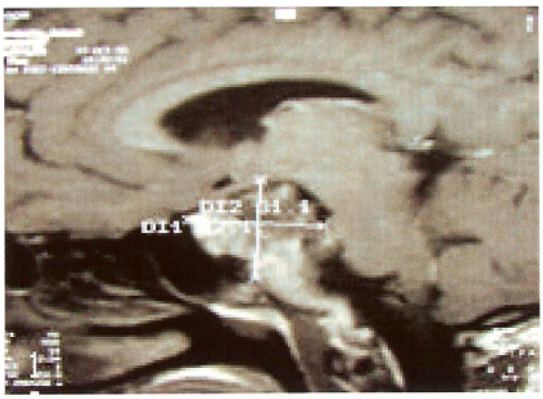

Figure 1. Sagittal contrast-enhanced magnetic-resonance image showing an irregular and heterogenous lesion associated with bony expansion above and posterior to the clivus encroaching upon the sella turcica, suggestive of chordoma.

infundibulum appeared displaced anterolaterally. The suprasellar cistern was partially obliterated and the superior margin of the lesion barely abutted upon the left optic tract and the vicinity of the optic chiasm. This presentation was suggestive of chordoma. An excisional transphenoidal biopsy confirmed the diagnosis, showing loosely arranged tumor cell cords and lobules separated by mucoid material. The tumor cells had cytoplasmic vacuoles with prominent vesicular nuclei and bubbly "physalipherous" appearance, characteristic of chordoma (Figure 2). Gamma knife radiosurgery was given to the

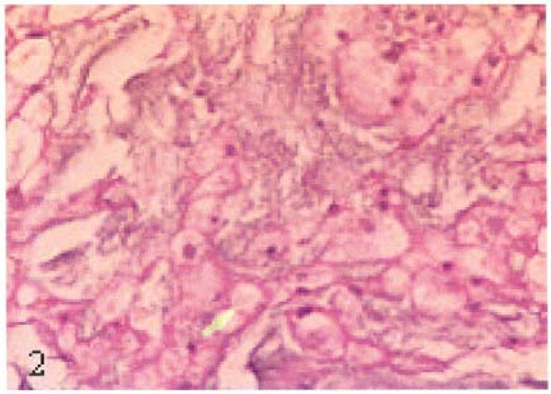

Figure 2. Bone biopsy with tumor cells having cytoplasmic vacuoles (arrow) with prominent vesicular nuclei and bubbly "physalipherous" appearance (hematoxylin-eosin stain, original magnification x40).

residual tumor and concern related to the role of azathioprine in the development of the chordoma prompted discontinuation of the drug. The patient discontinued other medications on her own. Surprisingly, her CD symptoms disappeared, she gained 15 pounds, and her hemoglobin level stabilized within normal limits. Clinical remission of CD was sustained for one year, at which time the disease relapsed. Azathioprine was restarted along with other medications; since then, she has required multiple hospitalizations due to CD exacerbations.

The patient has moderate to severe active CD involving the entire left colon from the transverse down to the anus and a transverse colon stricture, with mild proximal dilatation, is present. A colon biopsy showed crypt distortion, as evidence of chronicity. Abundant inflammatory cells within the lamina propria, cryptitis, and crypt abscesses were also present, evidencing activity of CD (Figure 3). No dysplasia was present. Abdomino-pelvic computed tomography scan showed concentric thickening of the colonic wall with changes more prominent from the mid portion of the transverse colon extending to the rectosigmoid portion with associated surrounding inflammatory fat stranding (Figure 4). High-dose infliximab therapy (10 mg/kg) resulted in a partial remission and allowed corticosteroid weaning. She continued receiving treatment with mesalamine and azathioprine, achieving

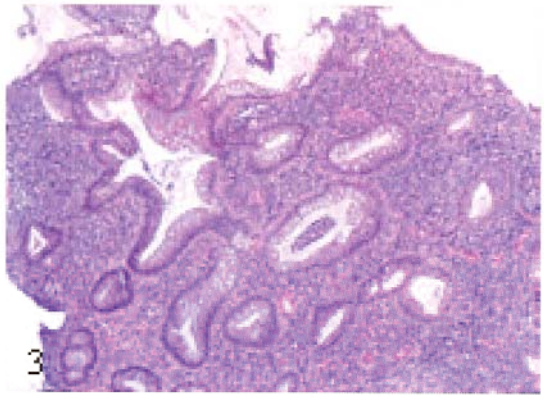

Figure 3. Colon biopsy with crypt distortion, abundant inflammatory cells within the lamina propria, cryptitis, and crypt abscesses (hematoxylin-eosin stain, original magnification x10).

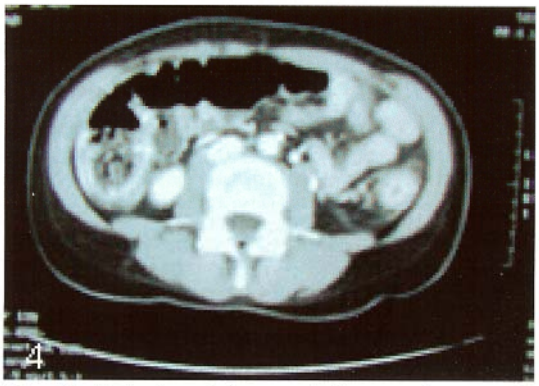

Figure 4. Abdomino-pelvic computed tomography scan, with contrast, showing concentric thickening of colonic wall with prominent changes from the mid portion of the transverse colon extending to the rectosigmoid portion with associated surrounding inflammatory fat stranding consistent with Crohn's colitis.

normal weight for her height (body mass index is 19.06 kg/m^2), although still with mild diarrhea, abdominal pain and normal hemoglobin levels. Infliximab was discontinued when she became pregnant. The pregnancy was complicated by symptomatic anemia, requiring transfusions. She delivered normal twins and has since resumed infliximab infusions. A recent MRI of the brain shows no evidence of recurrence of the chordoma.

Discussion

The patient we present has a typical CD clinical course and complications. She has been treated with multiple medications, including long-term azathioprine. Among all the medications used in our patient, azathioprine is the only one that has been associated to malignancy, primarily lymphoma (1-2). Several lymphomas have been reported after initiation of therapy with azathioprine. However, the risk seems to be small and it must be weighed against the likelihood of entering remission (1). The potentially increased risk of malignancy is controversial, since recent evidence suggests that azathioprine therapy for CD does not increase the risk of lymphoma (2). The fact that the patient developed a chordoma after prolonged azathioprine therapy raised concern. Until now, a specific trigger for the development of chordoma has not been identified and association to any medication has not been previously reported in the literature.

Cytogenetic studies on chordomas are limited, normal karyotypes or hypodiploidy have been demonstrated, most often occurring as loss of chromosomes 3, 4, 10, and 13 (4). A putative tumor suppressor locus in familial and sporadic chordomas is localized at 1p36 (4-5). Retinoblastoma tumor suppressor gene (13q14) has been linked to the pathogenesis of chordoma (4). Recurring aberrations in skull base chordomas are formation of isochromosome 1q, loss of 1p and 3p, gain of chromosomal regions 5q and 7q2, gain of chromosome 20, and loss of chromosome 18 (4, 6-7). A locus for familial chordoma has been mapped to 7q33 (8).

An association between CD and chromosomes 1 (1q), 6, 10, 12, and 16 (9-12) has been reported. Possible susceptibility genes located in these areas include intestinal secretory mucins (9) and immune-response genes (10). IBD has been linked to regions in chromosomes 1 (1p36), 3 (3p), 6, 7 (7q), 12, 22, and X (9-11, 13-14). Mutations in these genetic regions may cause defects in immune regulation or unique genes to the disease may determine the susceptibility of the gastrointestinal tract to the inflammatory response.

When the genetic associations of CD and chordoma were compared, we found that they both have abnormalities in chromosomes 1 (1q) and 10. Inflammatory bowel disease and chordoma have abnormalities in chromosomal regions 1p, 3p, and 7q, and different abnormalities occur in the same chromosomal regions. It is of interest that at chromosomal region 7q, chordoma shows a gain while IBD shows the presence of a susceptibility gene. This finding could lead to a speculative synergistic effect on the clinical expression of both chordoma and IBD. Further genetic studies, especially for chordoma, are needed to seek any similar genetic defect in shared chromosomal regions for CD and chordoma or IBD and chordoma.

The clinical remission from CD occurring after radiosurgery in our patient is of interest. Because the

radiation received for the chordoma is highly focused, it is very unlikely that it had any effect in inducing the remission of the CD. A coincidental spontaneous remission is the more likely explanation. The clinical course of CD is often erratic with a period of frequent relapses followed by periods of virtually complete remission. Munkholm et al (15) studied 373 CD patients with a mean follow-up of 8.5 years. They reported that the relapse-free course in CD was 12% after 10 years of disease and that the probability of a continuously active course without remission was 1% after 10 years (15). The patient we present had approximately 10 years of disease when she entered into CD remission. Fifty percent of the patients studied by Munkholm et al (15) were expected to stay in remission for an even longer period late in the disease course.

In this report we present the clinical picture and course of the first case reported in the literature of a chordoma associated to CD. Although there are chromosome anomalies occurring at the same chromosomes in both diseases, a direct relationship between development of this tumor and the presence of CD is speculative. Further studies in these conditions are needed to determine if there is a genetic association between them. The immunomodulating effect of azathioprine could not be directly associated to the etiology or development of chordoma. The clinical remission of CD after gamma knife radiosurgery may be explained by a coincidental quiescent stage of CD.

Resumen

La enfermedad de Crohn es una enfermedad inflamatoria del intestino caracterizada por remisiones y exacerbaciones. Los medicamentos inmunosupresores son usados frecuentemente para inducir y mantener remisión en estos pacientes. El uso del inmunomodulador azatioprina ha sido asociado a malignidades. Los cordomas son tumores raros y localmente agresivos que surgen de remanentes del notocordo. Un activador específico para este tumor no ha sido identificado y su asociación a algún medicamento no ha sido reportada. El propósito de este reporte es presentar el primer caso reportado en la literatura de enfermedad de Crohn asociado a un cordoma. El paciente a ser presentado estaba en terapia de azatioprina, entre otros medicamentos. Una revisión de literatura reveló que la enfermedad de Crohn y cordoma tienen ambos anormalidades en los cromosomas 1 y 10. La enfermedad inflamatoria del intestino y cordoma tienen ambos anormalidades en las regiones cromosomales 1p, 3p y 7q. A pesar de estos hallazgos, una relación genética directa entre estas enfermedades es puramente especulativa.

Acknowledgements

The authors thank Dr. María Santaella and Dr. Hernando Ortíz for their expert advise in this case report.

References

1. Stein RB, Lichtenstein GR. Medical therapy for Crohn's disease: the state of the art. Surg Clin North Am 2001;81:71-101.
2. Su C, Lichtenstein GR. Recent developments in inflammatory bowel disease. Med Clin North Am 2002;86:1497-1523.
3. Richardson MS. Pathology of skull base tumors. Otolaryngol Clin North Am 2001;34:1025-1042.
4. Sawyer JR, Husain M, Al-Mefty O. Identification of isochromosome 1q as a recurring chromosome aberration in skull base chordomas: a new marker for aggressive tumors? Neurosurg Focus [serial online]. March 2001; 10(3). Available from: American Association of Neurological Surgeons, Rolling Meadows, Il. Accessed February 11, 2003.
5. Miozzo M, Dalprà L, Riva P, et al. A tumor suppressor locus in familial and sporadic chordoma maps to 1p36. Int J Cancer 2000;87:68-72.
6. Scheil S, Bruderlein S, Liehr T, et al. Genome-wide analysis of sixteen chordomas by comparative genomic hybridization and cytogenetics of the first human chordoma cell line, U-CH1. Genes Chromosomes Cancer 2001;32:203-211.
7. Dalprà L, Malgara R, Miozzo M, et al. First cytogenetic study of a recurrent familial chordoma of the clivus. Int J Cancer 1999;81:24-30.
8. Kelley MJ, Korczak JF, Sheridan E, Yang X, Goldstein AM, Parry DM. Familial chordoma, a tumor of notochordal remnants, is linked to chromosome 7q33. Am J Hum Genet 2001;69:454-460.
9. Stotland, BR, Stein RB, Lichtenstein, GR. Advances in inflammatory bowel disease. Med Clin North Am 2000;84:1107-1124.
10. Hampe J, Schreiber S, Shaw SH, et al. A genomewide analysis provides evidence for novel linkages in inflammatory bowel disease in a large European cohort. Am J Hum Genet 1999;64:808-816.
11. Bonen DK, Cho JH. The genetics of inflammatory bowel disease. Gastroenterology 2003;124:521-536.
12. Ahmad T, Armuzzi A, Bunce M, et al. The molecular classification of the clinical manifestations of Crohn's disease. Gastroenterology 2002;122:854-866.
13. Satsangi J, Parkes M, Louis E, et al. Two stage genome-wide search in inflammatory bowel disease provides evidence for susceptibility loci on chromosomes 3, 7 and 12. Nat Genet 1996;14:199-202.
14. Hampe J, Lynch NJ, Daniels S, et al. Fine mapping of the chromosome 3p susceptibility locus in inflammatory bowel disease. Gut 2001;48:191-197.
15. Munkholm P, Langholz E, Davidsen M, Binder V. Disease activity courses in a regional cohort of Crohn's disease patients. Scand J Gastroenterol 1995;30:699-706.