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Case Report

Crohn's disease in a patient with von Recklinghausen's disease: A rare combination of two disorders with strong genetic background

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SUMMARY

We describe a very rare case of a patient with von Recklinghausen disease who developed Crohn's disease of the ileocecal region at the age of 56. To the best of our knowledge this is the first case described so far in the international literature. Case report: A man with known von Recklinghausen disease started having diarrhoea, abdominal pain and loss of weight at the age of 53. His grand mother, father and two of his three children (boys) also suffered from von Recklinghausen disease. Except for the typical skin lesions his children also developed congenital myopia, glaucoma and hypoplastic lower jaw. Physical examination revealed numerous cafe *au lai* spots, and subcutaneous nodules of various sizes scattered throughout the whole body, typical of von Recklinghausen disease. A painful mass was palpable in the right ileal fossa. The diagnosis of Crohn's disease was based on the findings of abdominal computed tomography (thickness of bowel wall and ileocecal area, enlargement of lymph nodes), enteroclysis (thickness of bowel folds, turbidity of mesenteric fat), colonoscopy (inflammatory lesions of the cecum and ileocecal valve) and histology of the ileocecal mucosa (severe inflammatory lesions compatible with Crohn's disease). Treatment with steroids and mesalamine resulted in prompt improvement of the situation. Since then the disease continued with exacerbations and remissions of mild to moderate severity which responded well to conservative treatment. The patient was operated on because of obstructive ileus due to the presence of a polypoid mass in the ileocaecal area. Histology of the resected specimen showed that the lesion was actually a large mass of pseudopolyps developing on the ground of Crohn's disease. A few months later his disease was complicated by development of thrombosis of the right subclavicular vein confirmed with Doppler ultrasound. His recovery was uneventful. *It is concluded* that Crohn's disease could appear on the ground of von Recklinghausen disease. The concurrent existence of the two situations is probably the result of chance. However, this combination of two diseases with strong genetic background further emphasizes the importance of genetic factors involved in the etiopathogenesis of Crohn's disease.

Key words: Von Recklinghausen's disease, Crohn's disease, inflammatory bowel disease

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INTRODUCTION

Neurofibromatosis type-1 (NF-1), also known as von Recklinghausen disease, is a common autosomal dominant condition occurring in approximately 1/3000 births. NF-1 is known to be associated with gastrointestinal neoplasms in 2-25% of patients.[1-6] The hallmark feature is the occurrence of neurofibromas, although other tumors including optic gliomas and malignant peripheral nerve sheath tumors can be found. There are also non-tumor manifestations, such as skeletal dysplasia and learning disabilities. Virtually all organ systems can be involved, either directly or through neural or vascular influences.

Gastrointestinal involvement in NF-1[7-11] occurs in three principal forms: hyperplasia of the submucosal and myenteric nerve plexuses and mucosal ganglioneuromato-

sis which leads to disordered gut motility; gastrointestinal stromal tumours showing varying degrees of neural or smooth muscle differentiation; and a distinctive glandular, somatostatin-rich carcinoid of the periampullary region of the duodenum which may be associated with phaeochromocytoma.

Crohn's disease (CD) is an inflammatory bowel condition with strong genetic background. Development of inflammatory bowel disease in patients with NF-1 has rarely been described.[12,13]

The aim of this presentation is to describe a patient with NF-1 who developed CD at the age of 56. To the best of our knowledge coexistence of the two diseases in the same patient has never previously been described.

CASE REPORT

A man with known NF-1 started having diarrhea, abdominal pain and loss of weight at the age of 53. His grand mother, father and two of his three children (boys) were also suffering from NF-1. Except for the typical skin lesions his children also have congenital myopia, glaucoma and hypoplastic lower jaw. Physical examination of the patient revealed numerous cafe *au lai* spots, and subcutaneous nodules of various size scattered in the whole body, typical of NF-1 (Figure 1). A painful mass was palpable in the right ileal fossa. The diagnosis of CD was based on the findings of computed tomography of the abdomen (thickness of bowel wall and ileocecal area, enlargement of lymph nodes), enteroclysis (thickness of bowel folds, turbidity of mesenteric fat), colonoscopy (inflammatory lesions of the cecum and ileocecal valve) and histology of the mucosa of ileocecal area (severe inflammatory lesions compatible with CD). Treatment with steroids and mesalamine resulted in prompt improvement of the situation. Since then the disease continued with exacerbations and remissions of moderate severity responding well to conservative treatment. The patient was finally operated on because of obstructive ileus due to the presence of an inflammatory mass in the ileocaecal area. On operation a right hemicolectomy with resection of the terminal ileum and end-to-end anastomosis was performed. Histology of the resected specimen showed that large parts were involved in CD and that the lesion in the cecum was in fact a large mass of pseudopolyps developing on the ground of CD. A few months later his disease was complicated by development of a thrombosis of the right subclavicular vein. However, his recovery was uneventful. The patient is under close surveillance.

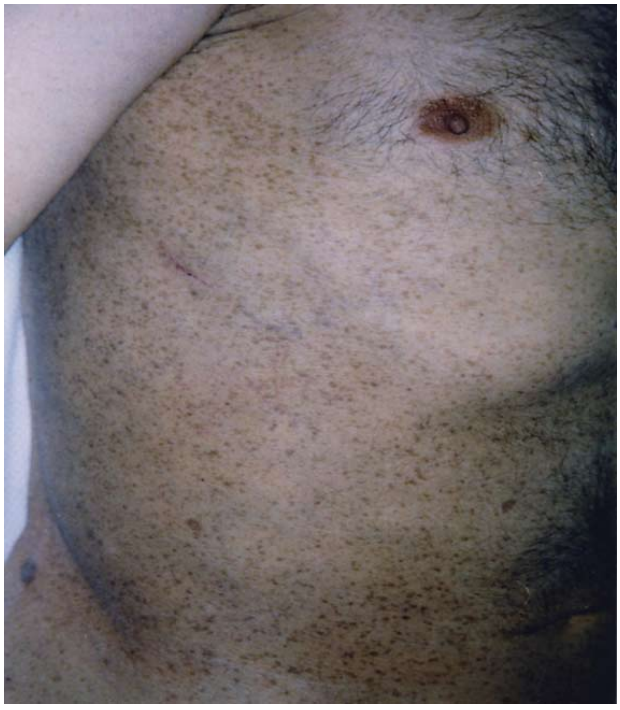

Figure 1.

DISCUSSION

In this report, we describe a patient with known NF-1 who developed CD at the age of 56. This combination has never been described, although coexistence of NF-1 with ulcerative colitis has previously been noticed[13]. Both diseases exhibit a strong genetic element including some other characteristics such as tumor formation.

NF1 accounts for about 90% of all cases of NF. Fifty percent of patients have a positive family history. In the remaining 50% the disorder represents a sporadic new mutation of the NF1 gene.[14]

The clinical expression of NF1 is extremely variable. Many of the clinical and neoplastic manifestations are age dependent, and they may vary among the affected members of a single family. Patients with NF1 are afflicted with a diverse group of lesions that are predominantly neuroectodermal or mesenchymal in origin. Benign or malignant tumors may be found in the brain, spinal cord, and somatic and autonomic peripheral nerves. Malignant tumors may involve the airway, the gastrointestinal tract, the genitourinary tract, and the blood vessels.[4] Gastrointestinal neoplasms are usually located in the small intestine (72%). Neurofibromas, are the most frequently diagnosed benign neoplasms (52%), followed by leiomyomas (13%), ganglioneurofibromas (9.8%), and gastrointestinal

stomal tumor (6.5%).[5] Oral manifestations can be found in almost 72% of patients.[7] The radiological appearances of NF-1 are numerous and variable, because of the widespread presence of peripheral nerves. Interestingly enough in our patient the most predominant clinical signs were only those related to skin lesions.

Concerning genetics, NF1 is considered to be an autosomal dominant condition caused by mutations of the NF1 gene, which is located at chromosome 17q11.2. It is believed to be completely penetrant.[15,16] A wide variety of NF1 mutations has been found in patients with NF1, but no frequently recurring mutation has been identified. Mutations range from single nucleotide substitutions to large-scale genomic deletions dispersed throughout the gene. Currently there is no obvious relationship between particular NF1 mutations and the resulting clinical manifestations. Laboratory testing for NF1 mutations is difficult. A protein truncation test is commercially available, but its sensitivity, specificity, and predictive value have not yet been established[14]. The role of *ras* in the pathogenesis of tumors in NF1 has suggested an approach to treatment using *ras* inhibitors.[17]

On the other hand the pathogenesis of CD is believed to be related to interactions between environmental, immunological and genetic factors. The latter is equally important with immunological abnormalities being present in all patients with CD. It is well established that NOD2 mutations are associated with the development of CD. As a pathogen-recognition molecule for muramyl dipeptide, NOD2 controls both innate and adaptive immune responses, through the regulation of cytokines, chemokines and antimicrobial peptides production[18]. Two other non-IBD diseases have been associated with NOD2 mutations[19]. The first is a rare disease long known to map to the pericentromeric region of chromosome 16 that has also been shown to carry mutations in NOD2 that result in the simple Mendelian inheritance of Blau syndrome. The second association has been shown with gastrointestinal Graft versus Host disease in which the course is exacerbated in the recipient if either donor or host carries any of the three risk alleles associated with CD. In addition a number of inherited autoimmune diseases have been shown to demonstrate linkage to the pericentromeric region of chromosome 16 that houses NOD2, including rheumatoid arthritis and lupus erythematosus.

Obviously there is no relation between either NF1 gene located on chromosome 17 encoding neurofibromin that controls cellular proliferation through interactions with *ras* oncogenes in von Recklinghousen disease and chromosome 16 carrying mutations of NOD-2 in CD patients. In the latter it is believed that the impaired and mutant NOD2 could lead to increased adaptive immune response and chronic intestinal inflammation.

The course of CD in our patient was quite unfavorable with exacerbations, one of which required surgical excision of a large part of the terminal ileum and cecum including a large polypoid lesion. Preoperatively this lesion was thought to be a malignant tumor developing on the ground of either CD or von Recklinghausen disease. The course of CD in our patient was further complicated due to development of venous thrombosis of subclavicular vein that fortunately responded well to conservative treatment.

Treatment of von Recklinghausen disease with plexiform neurofibromas has been empiric, with surgery being the primary option for those with progressive lesions causing a major degree of morbidity. More recently, biologic-based therapeutic approaches, using drugs that target the molecular genetic underpinnings of plexiform neurofibromas or cytokines believed important in tumor growth, have been initiated[20]. No such treatment was applied to our patient.

The average life expectancy of patients with NF1 is probably reduced by 10-15 years, and malignancy is the most common cause of death.

In conclusion, CD can appear on the ground of von Recklinghausen disease. The concurrent existence of the two situations is probably the result of chance. However, this combination of disorders with strong genetic background underlines once again the significance of genetic factors in the etiopathogenesis of CD.

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