Diarrhoea, Hyperpigmentation and Hamartomatous Polyposis Syndrome

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Abstract
Cronkhite-Canada syndrome (CCS) is a rare, non-hereditary hamartomatous polyposis syndrome of unknown aetiology. It is characterized by diffuse gastrointestinal polyps, dystrophic nail changes, alopecia, cutaneous hyperpigmentation, chronic diarrhoea, anorexia and hypogeusia. It is associated with a high incidence of gastrointestinal malignancies, mortality and morbidity. Early clinical suspicion and treatment is important. We report an elderly male with CCS who showed clinical and endoscopic improvement with long term corticosteroid therapy.

Introduction
Cronkhite and Canada first described this syndrome in 1955. It is a rare, nonfamilial disorder associated with gastrointestinal polyposis mostly hamartomatous, chronic diarrhoea, cutaneous hyperpigmentation, alopecia, onychodystrophy and weight loss. Etiology is still unknown but may be immune-mediated since it responds to immunosuppressive therapy. It has a high morbidity and mortality. Treatment includes nutritional support, glucocorticoids, azathioprine, acid suppression and antibiotics, but there is no consistently recommended therapy.

Case Report
A 56 year old, farmer was symptomatic since 1 year for repeated episodes of watery diarrhoea, (voluminous, around 10 - 12 times per day), progressive hyperpigmentation of face, extremities and trunk, associated with loss of appetite and weight. There was no significant past history or family history. Physical examination revealed hyperpigmentation all over the body with no mucosal involvement. He had frontal alopecia, loss of eye brows & axillary hair, and dystrophic changes of nails (Figure 1). Laboratory parameters were normal except a low serum albumin of 2.8 gm/dl. C-reactive protein was also normal. Esophagogastroduodenoscopy (EGDscopy) showed normal oesophagus, thickened nodular gastric folds with multiple sessile polyps in the duodenum. There were multiple sessile polyps from caecum to rectum on colonoscopy, largest measuring around 1 x 1 cm in the caecum (Figure 2). On histopathology, gastric, duodenal and colonic biopsies revealed hamartomatous polyps showing villi flattening and cystic dilatation of glands. Lamina propria was edematous and filled with mixed inflammatory infiltrate predominantly eosinophils (Figure 3). On the basis of clinical features and histopathological findings of hamartomatous polyps in the gastrointestinal tract, a diagnosis of Cronkhite Canada syndrome was made. Patient was started on nutritional support and oral prednisolone 40 mg daily which was to be tapered slowly over 1 year. Patient had symptomatic improvement in diarrhoea, reduced hyperpigmentation and no further worsening in dystrophic nails and hair at 2 month follow up. He unfortunately stopped treatment and was lost to follow up. Six months later he presented again with similar complaints. He was restarted on nutritional support and steroid therapy on which he showed improvement within 3 months but has not followed up thereafter.

Discussion
Until now more than 500 cases of CCS have been reported worldwide. Reports have been from Europe or Asia (mainly Japan) and the incidence of CCS is one per million. It is a hamartomatous polyposis syndrome of undefined etiology characterized by disturbances in epithelia of gastrointestinal tract and epidermis. Patients present in fifth to sixth decades of life and male to female ratio is 1.8:1. An underlying immune mechanism is a possibility as the syndrome is associated with other autoimmune diseases, ANA may be positive and presence of IgG4 antibody in the polyps with response to immunosuppressants has been reported. Physical exertion and mental stress may trigger this syndrome. Familial predisposition is unlikely and there is only one report of CCS in a father and son of Indian origin.

It is characterized by diffuse gastrointestinal polyps, chronic diarrhoea, and protein losing enteropathy with dystrophic skin and nail changes. Goto has divided this disease into five types based on the onset of clinical features: Type I: diarrhoea as initial symptom (35.4%); Type II: dysguesia (40.9%); Type III: dominated by dry mouth (6.4%); Type IV: hair loss and nail atrophy (9.1%); and Type V: loss of appetite and malaise, followed by nail atrophy, hair loss but no diarrhoea (8.2%). Our patient presented as Type I CCS. Polyposis is seen in 52 to 96% of patients and they are distributed in the entire gastrointestinal tract. In contrast to prior reports the
oesophagus was involved in 12.3% of the cases. Hamartomatous polyps are the most common but inflammatory, adenomatous and hyperplastic polyps can also be seen. Murcosa in between the hamartomatous polyps shows features of inflammation. Adenomatous epithelium foci can lead to malignancy. Risk of gastric carcinoma is 5% and colorectal carcinoma is 9% with sigmoid colon and rectum being the common sites. Endoscopic surveillance annually is recommended in these patients. Because polyps have malignant potential, some experts suggest resection of all polyps that are >1 cm in diameter. Similar to our case thickened hypertrophic gastric folds mimicking Menetrier’s disease with polypoid lesions has been reported. Hyperpigmentation is usually found in neck, face, palms and soles. The cutaneous features are attributed to malnutrition or immune mediated and they may precede the gastrointestinal symptoms. Diagnostic endoscopic findings suggest increased IgG4 plasma cells.

Treatment regimens reported in the literature are variable. Corticosteroid, Anabolic steroids, various antibiotics, dietary supplementation, Ranitidine, Cromolyn sodium, Mesalazine or 5-amino salicylic acid and symptomatic treatment have all been used. Steroid therapy and nutritional support are the mainstays of medical treatment. The currently recommended high-dose prednisolone ≥ 40 mg/day is optimal for active CCS. Average duration for clinical improvement and polyp regression is around 12 months. Steroids should be tapered after endoscopic confirmation of polyp regression. Rapid steroid reduction can cause early relapse. Sustained endoscopic remission has been associated with reduced cancer risk. Steroid-sparing therapies such as Azathioprine, cyclosporine, anti-TNF-alpha agent, can be used in steroid-resistant cases in order to induce or maintain clinical remission. Surgery is reserved for bowel complications, such as severe protein-losing enteropathy, persistent haematochezia, malignant transformation and for reducing polyp burden. Mortality rate is up to 55%, frequently due to complications like anemia, gastrointestinal bleeding, congestive heart failure, septicaemia, intussusception and osteoporotic fractures.

Conclusion
Clinicians should be vigilant about CCS in patients with unexplained diarrhoea, gastrointestinal polyposis and ectodermal abnormalities.

References