Elizabeth Montgomery

Case . Slide 893. This adult patient had diarrhea. The requisition stated “rule our celiac disease”.

Diagnosis – Autoimmune enteropathy

AUTOIMMUNE ENTEROPATHY

This rare condition is characterized by 1) small intestinal villous atrophy *unresponsive to dietary restrictions*, 2) unrelenting diarrhea, and 3) predisposition to autoimmune disease, as initially proposed by Unsworth and Walker-Smith(1). Though initially thought to affect newborns and young children, adult onset is well-documented in the literature [94-97]. Pathophysiology is poorly-understood but a proposed mechanism involves loss of self-tolerance and a hypereactive immune system with innapropriate T-cell activation and cytotoxicity. Increased numbers of mucosal CD4+ and CD8+ T cells have been observed by some. This activation may be a result of aberrant HLA class II molecule expression in enteric crypt epithelial cells (normally expressed only by mature enterocytes) as documented by Mirakian et al.(2). Certain autoantibodies are associated with this condition namely, anti-goblet cell and anti-enterocyte antibodies. Akram et al. found these antibodies in 13 out of 14 (93%) studied patients. Their presence, however, seems neither necessary nor sufficient for disease development as some patients with the condition have no detectable antibodies and antibodies have been detected in healthy subjects and in patients with celiac disease. Additionally, a myriad of other autoantibodies may be present or coexist with the gut-specific antibodies namely, anti-nuclear, anti-striated muscle, anti-parietal, anti-SSA, and anti-phospholipid antibodies, to name a few. Up to 87% of affected patients suffer from associated autoimmune disorders such as rheumatoid arthritis, myasthenia gravis, psoriatic arthritis, hypothyroidism, autoimmune inflammatory myopathy, idiopathic thrombocytopenic purpura, Raynaud phenomenon, and atrophic gastritis, among others. Two variants of the disorder are described. The first, termed IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) syndrome, is fatal, X-linked and characterized by polyendocrinopathy and various autoimmune conditions in association with severe, prolonged diarrhea(3-4). The second, termed APECED (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy) syndrome or APS-1 (autoimmune polyglandular syndrome 1) is autosomal recessive and affected patients suffer from autoimmune enteropathy in association with endocrine abnormalities (hypoparathyroidism, adrenocortical insficiency, diabetes mellitus, thyroid disease), mucocutaneous candidiasis, and skin manifestations such as alopecia and vitiligo, and nail deformities.

The histologic appearance of autoimmune enteropathy varies considerably from case to case. Intestinal biopsies show a picture similar to celiac disease with total or partial villous atrophy, crypt hyperplasia, and expansion of the lamina propria by a lymphoplasmacytic infiltrate. Some cases display intact villous architecture. Active inflammation with or without crypt abscesses may or may not be present. Increased intraepithelial lymphocytes may be seen but often to a lesser degree than in celiac disease. Crypt apoptotis is striking in some cases. Goblet and/or Paneth cells may be absent. Cases lacking goblet cells and/or Paneth cells are

easy to recognize as autoimmune enteropathy if the pathologist is in the habit of assessing for these components in biopsies whereas the diagnosis can only be listed as part of a differential diagnosis when, for example, prominent apoptosis is the most salient feature. The diagnosis should be considered when examining biopsies from adult patients labeled as having “refractory sprue” and from babies and children with intractable diarrhea. Treatment consists of nutritional support and immunosuppressive therapy. With treatment, some patients with absent goblet and Paneth cells regain them.

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2. Mirakian R, Hill S, Richardson A, Milla PJ, Walker-Smith JA, Bottazzo GF. HLA product expression and lymphocyte subpopulations in jejunum biopsies of children with idiopathic protracted diarrhoea and enterocyte autoantibodies. J Autoimmun. 1988 Jun;1(3):263-77.
3. Blanco Quiros A, Arranz Sanz E, Bernardo Ordiz D, Garrote Adrados JA. From autoimmune enteropathy to the IPEX (immune dysfunction, polyendocrinopathy, enteropathy, X-linked) syndrome. Allergol Immunopathol (Madr). 2009 Jul-Aug;37(4):208-15.
4. d'Hennezel E, Ben-Shoshan M, Ochs HD, Torgerson TR, Russell LJ, Lejtenyi C, et al. FOXP3 forkhead domain mutation and regulatory T cells in the IPEX syndrome. N Engl J Med. 2009 Oct 22;361(17):1710-3.