

Leukaemia Section

Short Communication

Alpha heavy chain disease

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Abstract

Alpha heavy chain disease (HCD) is the most prevalent form of heavy chain diseases, a rare family of syndromes associated with or representing a B cell malignancy variant. The hallmark characteristic and the pathogenic mechanism of HCD is the synthesis of a mutant, misfolded immunoglobulin heavy chain (IgH) which cannot form a quaternary conformation with the immunoglobulin light chain (IgL) and/or be degraded by the proteasome. The isotype of mutated IgH (α, γ or μ) determines the nomenclature of HCD subtypes. More than 400 cases of alpha HCD have been reported in the literature. The distinct epidemiology of the disease, affecting low socio-economical status individuals in the Mediterranean, North Africa, and Middle East, suggests an environmental etiologic agent. It typically affects individuals in their second and third decade of life, with a slight male predominance. Alpha HCD typically involves the small intestine (predominantly duodenum and jejunum), and presents as a malabsorption syndrome with symptoms and signs related to the severity and duration of involvement. A lymphomatous variant with predominant involvement of lymph nodes, spleen, and liver; as well as a respiratory variant with diffuse pulmonary infiltrates and restrictive pattern of respiratory function, have been reported. Diagnosis is based on laboratory findings and histologic analysis of involved organs. Based on the probable infectious pathogenesis, emphasis is on primary prevention via improvement of sanitary conditions and hygiene. Left untreated, alpha HCD locally progresses and eventually spreads systemically. A prolonged trial (>

6 months) of antimicrobial therapy is the first therapeutic approach even in the absence of a documented pathogen, followed by abdominal radiation and/or doxorubicin-based combination chemotherapy regimens plus minus surgical debulking. The five year overall survival rate after combination chemotherapy is 67%. Autologous hematopoietic stem cell transplantation should be considered in patients with relapsed/refractory disease.

Keywords

alpha heavy chain disease; B cell malignancy; IPSID, immunoglobulin heavy chain

Identity

Other names

α HCD

Note

Alpha heavy chain disease (HCD) is the most prevalent form of heavy chain diseases, a rare family of syndromes associated with or representing a B cell malignancy variant. (Seligmann et al., 1968; Ferman and Brouet, 1999; Bianchi et al., 2014) The hallmark characteristic and the pathogenic mechanism of HCD is the synthesis of a mutant, misfolded immunoglobulin heavy chain (IgH), which cannot form a quaternary conformation with the immunoglobulin light chain (IgL) and/or be degraded by the proteasome. (Goossens et al., 1998; Munshi et al., 2008) The isotype of mutated IgH (α, γ or μ) determines the nomenclature of HCD subtypes. (Harris NL, 2008)

Clinics and pathology

Alpha HCD typically involves the small intestine (predominantly duodenum and jejunum) and presents as a malabsorption syndrome with symptoms and signs related to the severity and duration of involvement. Abdominal discomfort, diarrhea, weight loss, anasarca, and ascites are typically present. (Doe et al., 1972) Patients commonly report nausea and emesis, while alopecia, amenorrhea, and growth retardation can be present in severe cases. Common laboratory findings are mild-to-moderate hypochromic anemia; hypocalcemia; hypokalemia; hypomagnesemia, and generalized vitamin and mineral deficiencies. Intestinal isoform of alkaline phosphatase is typically elevated. Microbiologic studies on biopsy or stool specimens should be done to rule out an overt infectious agent. Indeed, *Campylobacter Jejuni* has been isolated in some cases of alpha HCD, although a clear etiopathogenic relationship between *C. Jejuni* infection and alpha HCD has not been clearly established. Upper endoscopy is the diagnostic test of choice, given the common involvement of duodenum and jejunum. Five different histologic patterns of digestive mucosa involvement have been reported: infiltrative, nodular, ulcerative, mosaic, and isolated fold thickening; infiltrative and nodular are the most specific and sensitive for diagnosis. (Halphen et al., 1986) Patients with lymphomatous variant of alpha HCD present with generalized lymphadenopathies and hepatosplenomegaly, while dyspnea and hypoxemia in the context of diffuse pulmonary infiltrates and restrictive pattern of respiratory function is the typical clinical presentation of respiratory variant of alpha HCD. (Stoop et al., 1971; Takahashi et al., 1988) Hilar adenopathy, skin rash, and peripheral blood eosinophilia have been reported in respiratory variant of HCD.

The abnormal Ig alpha heavy chain can manifest as hypogammaglobulinemia or a normal serum protein electrophoresis (SPEP). A broad monoclonal band migrating in the $\alpha 2$ - β region may be present and identified via immunofixation with anti IgA serum. The lymphoma variant associated with alpha HCD resembles mucosa-associated lymphoid tissue (MALT), and immunoproliferative small intestine disease (IPSID) has been diagnosed in this context. Pathologic analysis of IPSID reveals a dense lymphoplasmacytic infiltrate of plasma cells admixed with small B lymphocytes separating the crypts and causing villous atrophy. Lymphoplasmacytic cells are monoclonal for cytoplasmic alpha chain in the absence of a light chain; plasma cells are CD138+ and CD20 negative; while small B lymphocytes express pan B-cell markers and lack CD5 and CD10.

Disease

Topography (ICD-O3): typical form: C17 and C26.0; Small intestine, intestinal tract. Respiratory variant: C39.9; Respiratory tract. Lymphomatous variant: C77.9, C22.0, C42.2; Lymph nodes, liver, spleen.

Phenotype/cell stem origin

Variant of lymphoplasmacytic lymphoma, resembling mucosa-associated lymphoid tissue lymphoma (MALT)

Etiology

Deletions, insertions or point mutations in the constant 1 (CH1) domain of the IgH are acquired during the process of somatic hypermutation. These mutations typically result in: 1- inability to bind and form a quaternary structure with IgL chain; and 2- inability to bind to the chaperone heat shock protein 78 (HSP 78) which mediates proteasomal degradation of free IgH. As a result, free IgH can be detected in both serum and urine. Although an infectious etiologic agent is suspected, none have been definitively identified to date. (Seligmann, 1975)

Epidemiology

Predominantly low socio-economical status individuals in their 20s-30s in the Mediterranean, North Africa, and Middle East are affected, with a slight male predominance. (Wahner-Roedler and Kyle, 2005)

Clinics

Alpha HCD typically involves the small intestine (predominantly duodenum and jejunum) and presents as a malabsorption syndrome with symptoms and signs related to the severity and duration of involvement. Abdominal discomfort, diarrhea, weight loss, anasarca, and ascites are typically present. (Doe et al., 1972) Patients can report nausea and emesis, while alopecia, amenorrhea, and growth retardation are present in severe cases. Common laboratory findings are mild-to-moderate hypochromic anemia; hypocalcemia; hypokalemia; hypomagnesemia; and generalized vitamin and mineral deficiencies. (Bianchi et al., 2014) Intestinal isoform of alkaline phosphatase is typically elevated. Microbiologic studies of biopsy or stool specimens should be conducted to rule out the presence of an overt infectious agent. (Parsonnet and Isaacson, 2004) Indeed, *Campylobacter Jejuni* has been isolated in some cases of alpha HCD, although a clear etiopathogenic relationship between *C. Jejuni* infection and alpha HCD has not been clearly established. (Lecuit et al., 2004; Peterson, 2004) Upper endoscopy is the diagnostic test of choice, given the common involvement of duodenum and jejunum.

Five different histologic patterns of digestive mucosa involvement have been reported: infiltrative, nodular, ulcerative, mosaic, and isolated fold thickening; infiltrative and nodular are the most specific and sensitive for diagnosis. (Halphen et al., 1986) Patients with lymphomatous variant of alpha HCD present with generalized lymphadenopathies and hepatosplenomegaly; while dyspnea and hypoxemia in the context of diffuse pulmonary infiltrates and restrictive pattern of respiratory function is the typical clinical presentation of respiratory variant of alpha HCD. Hilar adenopathy, skin rash, and peripheral blood eosinophilia have been reported in the respiratory HCD variant. (Stoop et al., 1971; Takahashi et al., 1988)

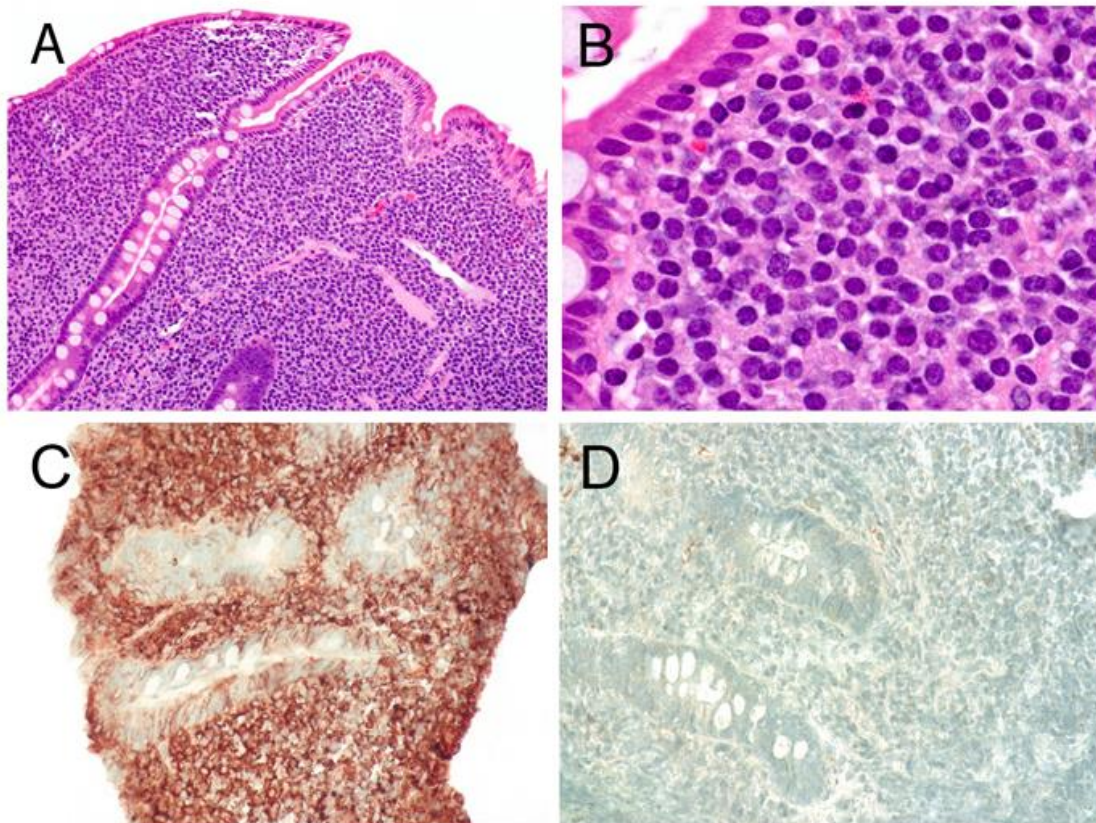
Pathology

The abnormal Ig alpha heavy chain can manifest as hypogammaglobulinemia or result in a normal serum protein electrophoresis (SPEP).

A broad monoclonal band migrating in the $\alpha 2$ - β region may be identified via immunofixation with anti IgA serum.

The lymphoma variant associated with alpha HCD resembles mucosa-associated lymphoid tissue (MALT) and has been defined as immunoproliferative small intestine disease (IPSID) in this context. (Al-Saleem and Al-Mondhiry, 2005) Pathologic analysis of IPSID reveals a dense lymphoplasmacytic infiltrate of plasma cells admixed with small B lymphocytes separating the crypts and causing villous atrophy (Isaacson et al., 1989; Fine and Stone, 1999).

Lymphoplasmacytic cells are monoclonal for cytoplasmic alpha chain in the absence of a light chain; plasma cells are CD138+ and CD20 negative; and the small B lymphocytes express pan B-cell markers and lack CD5 and CD10 expression. (Wahner-Roedler and Kyle, 1992; Fine and Stone, 1999)



Panel A: Low magnification view of H&E staining of duodenal biopsy in a patient with alpha HCD shows dense lymphocytic infiltration of lamina propria, associated with blunting of villous structures and spreading of crypts. **Panel B:** Higher magnification view of pathologic specimen in A shows lymphocytic infiltrate to be predominantly comprised of atypical plasma cells with characteristic relatively abundant eosinophilic, pink cytoplasm, eccentric nuclei, and dispersed chromatin. Upon immunohistochemistry (IHC) staining, plasma cells are largely positive for IgA (**Panel C**) and negative for IgM (**Panel D**), distinguishing alpha HCD infiltrate from classical MALT. IHC staining for κ and λ light chains was negative on this specimen (panel not shown). Panels C and D from Dr. Judith A. Ferry, Massachusetts General Hospital. Reproduced with permission from Bianchi et al. *Oncology*, 2014;28(1):45-53.

Cytogenetics

Unknown

Genes

Unknown

Treatment

Even in the absence of an identified infectious agent on biopsy or stool specimens, a prolonged trial (> 6 months) of broad antimicrobial therapy with ampicillin, metronidazole or tetracycline is generally recommended in an attempt to alleviate malabsorption symptoms. (1976) Antibiotic therapy should be appropriately tailored if an infectious agent is identified. Response rates to antibiotic therapy between 33% and 71% have been reported in early stage disease, although recurrence is frequent. (Ben-Ayed et al., 1989; Salem and Estephan, 2005) Total abdominal radiation or doxorubicin-based combination therapy are therapeutic options for refractory disease. CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), CHVP (cyclophosphamide, doxorubicin, teniposide and prednisone) and ABV (doxorubicin, bleomycin and vinblastine) have activity against refractory, advanced alpha HCD, and are superior to doxorubicin-free regimens such as COPP (cyclophosphamide, vincristine, procarbazine, and prednisolone). A CR rate of 64% with 5 year OS of 67% has been reported after treatment with combination chemotherapy. (Akbulut et al., 1997) Surgical debulking can be implemented following systemic chemotherapy, and high dose chemotherapy followed by autologous hematopoietic stem cell transplantation should be considered in patients with relapsed/refractory disease. (Martin and Aldoori, 1994)

Evolution

The natural history of alpha HCD is local progression leading to complications such as small bowel obstruction or perforation, followed by systemic spread systemically. (Bianchi et al., 2014)

Prognosis

The outcome is good in antibiotic-responsive, early disease. In the advanced disease and relapsed setting, a CR rate of 64% with 5 year OS of 67% has been reported after treatment with combination chemotherapy. (Akbulut et al., 1997)

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