

Leukaemia Section

Short Communication

Mu heavy chain disease

Giada Bianchi, Kenneth C. Anderson

LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Department of Medical Oncology, Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, 02115.
giada_bianchi@dfci.harvard.edu; kenneth_anderson@dfci.harvard.edu

Published in Atlas Database: June 2016

Online updated version : <http://AtlasGeneticsOncology.org/Anomalies/MuHeavyChainID1740.html>

Printable original version : <http://documents.irevues.inist.fr/bitstream/handle/2042/68177/06-2016-MuHeavyChainID1740.pdf>
DOI: 10.4267/2042/68177

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.
© 2016 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Abstract

Mu heavy chain disease (HCD) is the most rare variant of HCD, a 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. Less than 50 cases of mu HCD have been reported. The first two cases of mu HCD were described in the 1970s. The disease was diagnosed in men in their late fifties complaining of unremitting joint pain/stiffness. Mu HCD affects predominantly Caucasian men in their 5th-6th decades. Similar to the other HCD, the etiopathogenesis of mu HCD is unknown, but most patients have a concurrent lymphoproliferative disorder resembling chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). There are single case reports of mu HCD in association with myelodysplastic syndrome (MDS), systemic amyloidosis, and diffuse large B cell lymphoma (DLBCL). (Witzens et al., 1998; Kinoshita et al., 2004) Association of mu HCD with recurrent pulmonary infections, portal hypertension, systemic lupus erythematosus, and pancytopenia has also been described. (Wahner-Roedler and Kyle, 2005) Presenting symptoms/signs of mu HCD are secondary to the associated lymphoproliferative disorder: the majority of patients have splenomegaly; 75% patients present with hepatomegaly; and 40% patients have superficial lymphadenopathy. In the first case

reports of mu HCD and in 20% cases overall, patients presented with lytic bone lesions associated with lymphocytic infiltration of the bone marrow space.

A hypoproliferative anemia is the most common laboratory finding in mu HCD, followed by thrombocytopenia. Lymphocytosis can be present. While serum protein electrophoresis (SPEP) is typically normal, immunofixation (IF) detects monoclonal mu IgH in polymers of different sizes without an associated light chain. Biclinal gammopathy with the presence of a second, intact IgM has been reported. Cytologic examination of bone marrow aspirate smears typically shows plasma cells with prominent cytoplasmic vacuoles and small, round lymphocytes. Upon immunophenotypic analysis, pathologic cells are typically positive for CD19, CD20, CD38, and cytoplasmic IgM, but lack light chain expression. However, dim expression of CD5 and kappa light chain has been rarely reported. Given the paucity of cases, there is no standard treatment for mu HCD. Patients with a laboratory diagnosis of mu HCD who are otherwise asymptomatic can be managed expectantly without any active therapy. If a lymphoproliferative disorder is detected, treatment regimens have included: CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone); CVP (cyclophosphamide, vincristine and prednisone); as well as single agent cyclophosphamide or fludarabine. Prognosis is variable, with disease ranging from highly aggressive to more indolent. The reported median overall survival is 2 years (less than one month to over 10 years); importantly, delay in the diagnosis of mu HCD is common due to technical difficulties in detecting the pathologic IgH, thus leading to

underestimation of overall survival. A spontaneous remission of mu HCD has been reported.

Keywords

mu heavy chain disease; B cell malignancy; immunoglobulin heavy chain

Identity

Other names

μ HCD

Note

Mu heavy chain disease (HCD) is the least common form of HCD, a rare family of syndromes associated with or representing a B cell malignancy variant.(Fermand 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

Disease

Topography (ICD-O3): Disseminated form: C77.8, C42.2, C22.0; Lymph nodes of multiple regions, spleen, liver. Localized medullary disease: C42.1; Bone marrow. Localized extramedullary disease: C44.9, C07.9, C10.9, C69.0, C73.9, C26.9; Skin nos, parotid gland, oropharynx, conjunctiva, thyroid gland, gastrointestinal tract nos.

Note

Mu HCD affects predominantly Caucasian men in their 5th-6th decades.(Wahner-Roedler and Kyle, 2005) Similar to the other HCD, the etiopathogenesis of mu HCD is unknown, but most patients have a concurrent lymphoproliferative disorder resembling chronic lymphocytic leukaemia (CLL/SLL).(Witzig and Wahner-Roedler, 2002) There are single case reports of mu HCD in association with myelodysplastic syndrome (MDS), systemic amyloidosis, and diffuse large B-cell lymphoma DLBCL.(Wahner-Roedler and Kyle, 1992; Iwasaki et al., 1997; Witzens et al., 1998; Maeda et al., 2006) Association of mu HCD with recurrent pulmonary infections, portal hypertension, systemic lupus erythematosus, and pancytopenia has also been reported.(Wahner-Roedler and Kyle, 2005) Presenting symptoms/signs of mu HCD are secondary to the associated lymphoproliferative disorder: the majority of patients have splenomegaly, 75% patients present with hepatomegaly; and 40% patients have superficial

lymphadenopathy. In both the first case reports of mu HCD and in 20% of cases overall, patients presented with lytic bone lesions associated with lymphocytic infiltration of the bone marrow space.(Ballard et al., 1970; Forte et al., 1970).

A hypoproliferative anemia is the most common laboratory finding, followed by thrombocytopenia. Lymphocytosis can be present. While serum protein electrophoresis (SPEP) is typically normal, immunofixation (IF) detects monoclonal mu IgH in polymers of different sizes without an associated light chain.(Tamura et al., 2003; Maisnar et al., 2008) Biclinal gammopathy with the presence of a second intact IgM has been reported (Wahner-Roedler and Kyle, 1992).

Cytologic examination of bone marrow aspirate smears typically shows plasma cells with prominent cytoplasmic vacuoles, and small, round lymphocytes. Upon immunophenotypic analysis, pathologic cells are typically positive for CD19, CD20, CD38 and cytoplasmic IgM, but lack light chain expression. However, dim expression of CD5 and kappa light chain has been rarely reported.(Bianchi et al., 2014)

Phenotype/cell stem origin

Most typical pathologic variant resembles CLL/SLL.

Etiology

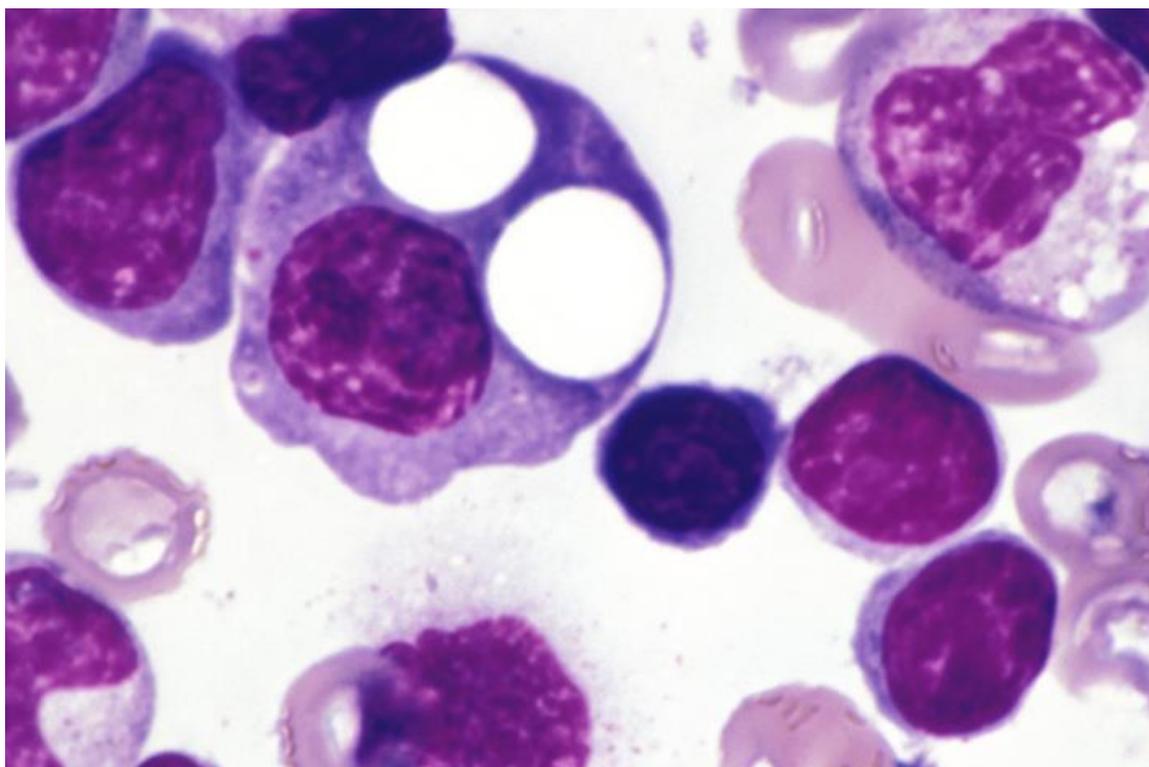
Deletions, insertions or point mutations in the constant 1 (CH1) domain of the IgH are acquired during the process of somatic hypermutation. These mutations typically result in: 1- inability to bind and form stable quaternary structure with IgL chain; and 2- inability to bind to the chaperone heat shock protein 78 (HSP 78) which mediates proteasomal degradation of free IgH. As a result, free IgH can be detected in both serum and urine. Pathogenesis is unknown.(Goossens et al., 1998)

Epidemiology

Mu HCD affects predominantly Caucasian men in their 5th-6th decades.

Clinics

Presenting symptoms/signs of mu HCD are secondary to the associated lymphoproliferative disorder: the majority of patients have splenomegaly, 75% patients present with hepatomegaly; and 40% patients have superficial lymphadenopathy. In both the first case reports of mu HCD and in 20% of cases overall, patients presented with lytic bone lesions associated with lymphocytic infiltration of the bone marrow space.(Ballard et al., 1970; Forte et al., 1970) A hypoproliferative anemia is the most common laboratory finding, followed by thrombocytopenia. Lymphocytosis can be present.(Bianchi et al., 2014)



High magnification view of H&E staining of bone marrow aspirate smear highlighting a plasma cell with prominent cytoplasmic vacuoles admixed with small, mature-appearing lymphocytes. Photo courtesy of Dr. Robert McKenna, University of Minnesota. Reproduced with permission from Bianchi et al. *Oncology*, 2014;28(1):45-53.

Pathology

While serum protein electrophoresis (SPEP) is typically normal, immunofixation (IF) detects monoclonal mu IgH in polymers of different sizes without an associated light chain.

Biclonal gammopathy with the presence of a second, intact IgM has been reported (Tamura et al., 2003; Maisnar et al., 2008). Cytologic examination of bone marrow aspirate smears typically shows plasma cells with prominent cytoplasmic vacuoles and small, round lymphocytes.

Upon immunophenotypic analysis, pathologic cells are typically positive for CD19, CD20, CD38, and cytoplasmic IgM, but lack light chain expression. However, dim expression of CD5 and kappa light chain has rarely been reported.

Treatment

Given the paucity of cases, there is no standard treatment for mu HCD (Witzig and Wahner-Roedler, 2002).

Patients with a laboratory diagnosis of mu HCD who are otherwise asymptomatic can be managed expectantly without any therapy.

If a lymphoproliferative disorder is detected, reported treatments include CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), CVP (cyclophosphamide, vincristine and prednisone), as well as single agent

cyclophosphamide or fludarabine (Yanai et al., 2004).

Prognosis is variable, with disease ranging from highly aggressive to more indolent.

The reported median overall survival is 2 years (less than one month to over 10 years); importantly, the diagnosis of mu HCD is common due to technical difficulties in detecting the pathologic IgH. A spontaneous remission of mu HCD has been reported.

Evolution

Variable. Patients with asymptomatic, incidental diagnosis of mu HCD can show no signs of lymphoproliferative disease for years/decades or progress to develop a lymphoproliferative disorder. The biologic behavior of the associated B cell malignancy ranges from indolent to highly aggressive.

Prognosis

Overall survival is highly variable and likely to be underestimated.

The reported median overall survival is 2 years (one month to over 10 years); importantly, delay in diagnosis of mu HCD is common due to technical difficulties detecting the pathologic IgH.

A spontaneous remission of mu HCD has been reported. (Wahner-Roedler and Kyle, 2005)

References

- Ballard HS, Hamilton LM, Marcus AJ, Illes CH. A new variant of heavy-chain disease (mu-chain disease). *N Engl J Med.* 1970 May 7;282(19):1060-2
- Bianchi G, Anderson KC, Harris NL, Sohani AR. The heavy chain diseases: clinical and pathologic features. *Oncology (Williston Park).* 2014 Jan;28(1):45-53
- Fernand JP, Brouet JC. Heavy-chain diseases. *Hematol Oncol Clin North Am.* 1999 Dec;13(6):1281-94
- Forte FA, Prelli F, Yount WJ, Jerry LM, Kochwa S, Franklin EC, Kunkel HG. Heavy chain disease of the gamma (gamma M) type: report of the first case. *Blood.* 1970 Aug;36(2):137-44
- Goossens T, Klein U, Küppers R. Frequent occurrence of deletions and duplications during somatic hypermutation: implications for oncogene translocations and heavy chain disease. *Proc Natl Acad Sci U S A.* 1998 Mar 3;95(5):2463-8
- Harris NL, I.P., Grogan TM, Jaffe ES.. Heavy chain diseases. 2008. In *WHO Classification of Tumours of the Haematopoietic and Lymphoid Tissues*. C.E. Swerdlow SH, Harris NL, et al., editor IARC, Lyon. 196-199.
- Iwasaki T, Hamano T, Kobayashi K, Kakishita E. A case of mu-heavy chain disease: combined features of mu-chain disease and macroglobulinemia *Int J Hematol* 1997 Oct;66(3):359-65
- Kinoshita K, Yamagata T, Nozaki Y, Sugiyama M, Ikoma S, Funachi M, Kanamaru A. Mu-heavy chain disease associated with systemic amyloidosis *Hematology* 2004 Apr;9(2):135-7
- Maeda A, Mori M, Torii S, Nagai Y, Togami K, Fujita H, Kurata M, Matsushita A, Nagai K, Imai Y, Takahashi T. Multiple extranodal tumors in mu-heavy chain disease *Int J Hematol* 2006 Oct;84(3):286-7
- Maisnar V, Tichy M, Stulik J, Urban P, Adam Z, Kadlckova E, Vavrova J, Palicka V, Jebavy L, Kodet R, Buchler T, Hajek R. Capillary immunotyping electrophoresis and high resolution two-dimensional electrophoresis for the detection of mu-heavy chain disease *Clin Chim Acta* 2008 Mar;389(1-2):171-3
- Munshi NC, Digumarthy S, Rahemtullah A. Case records of the Massachusetts General Hospital Case 13-2008 A 46-year-old man with rheumatoid arthritis and lymphadenopathy
- Tamura A, Yamashiro A, Mizutani F, Oita T, Maeda A, Takahashi T. [Immunochemical properties of free mu-chain protein in a patient with mu-heavy chain disease] *Rinsho Byori* 2003 Sep;51(9):847-51
- Wahner-Roedler DL, Kyle RA. Heavy chain diseases *Best Pract Res Clin Haematol* 2005;18(4):729-46
- Witzens M, Egerer G, Stahl D, Werle E, Goldschmidt H, Haas R. A case of mu heavy-chain disease associated with hyperglobulinemia, anemia, and a positive Coombs test *Ann Hematol* 1998 Nov;77(5):231-4
- Witzig TE, Wahner-Roedler DL. Heavy chain disease *Curr Treat Options Oncol* 2002 Jun;3(3):247-54
- Yanai M, Maeda A, Watanabe N, Sugimoto N, Matsushita A, Nagai K, Oida T, Takahashi T. Successful treatment of mu-heavy chain disease with fludarabine monophosphate: a case report *Int J Hematol* 2004 Feb;79(2):174-7

This article should be referenced as such:

Bianchi G, Anderson K. Mu heavy chain disease. *Atlas Genet Cytogenet Oncol Haematol.* 2017; 21(3):114-117.
