Non-Secretory Multiple Myeloma Relapsing as Extramedullary Liver Plasmacytomas

Rodrigo Lopes da Silva, Alexandra Monteiro, Joana Veiga

Serviço de Hematologia, Hospital Santo António dos Capuchos, Lisboa, Portugal

Abstract
We report a case of a 58-year-old woman with a true non secretory multiple myeloma of the producer type relapsing after many lines of therapy including the novel anti-myeloma drugs, which eventually relapsed as extramedullary liver plasmacytomas manifesting as a fatal acute cholestatic hepatitis. Due to the aggressiveness of this disease, new therapeutic modalities are necessary.

Keywords
Non-secretory multiple myeloma – extramedullary liver plasmacytoma – cholestatic hepatitis.

Introduction
Plasma cell neoplasms comprise a spectrum of diseases ranging from indolent conditions such as Monoclonal Gammopathy of Undetermined Significance (MGUS) to the more aggressive multiple myeloma (MM) and plasma cell leukemia.

Non-secretory multiple myeloma (NSMM) is a rare clinical and biological variant of the classic form of MM characterized by the absence of monoclonal immunoglobulins in either serum or urine electrophoresis and represents less than 1% of this spectrum [1].

Myelomatous infiltration of extra-osseous sites is relatively frequent on autopsy series (>70%) however clinical manifestations are rare pre-mortem [2]. Diffuse hepatic infiltration is a common finding (~50%), but the nodular form as liver plasmacytoma is a clinical rarity [3] and this finding is associated with a more aggressive form of MM (end-stage myeloma). The patients usually have poor outcomes even with more aggressive treatment approaches.

We report a case of a 58-year-old woman with a non secretory multiple myeloma relapsing after many lines of therapy, which eventually relapsed as aggressive extramedullary liver plasmacytomas manifesting as a cholestatic hepatitis.

Case report
A 58-year-old female patient was diagnosed in 2004 with a non-secretory multiple myeloma (Durie-Salmon stage IIIA, International Staging System-II) presenting initially as lytic lesions and a paravertebral lumbar plasmacytoma. She received a total of 40Gy radiotherapy with regression of the lesion. One year later, the patient relapsed with bone pain and hypercalcemia, with a bone marrow plasmacytosis of 13%. Chemotherapy was started using Vincristine (0.4 mg/day d1-4), Doxorubicin (9 mg/m²/day d1-4) and Dexamethasone (40mg/day d1-4) every 25 days for 3 cycles achieving a partial response, followed by high-dose Melphalan 200 mg/m² and autologous peripheral blood stem cell infusion with a complete response. Maintenance therapy was given with Thalidomide 100mg/day, but it was stopped a year later due to neurologic toxicity.

In 2007, the patient had a second relapse with systemic disease. Treatment was started with Bortezomib (1.3mg/m²) and Dexamethasone (20 mg) on days 1, 4, 8 and 11 for 6 cycles with a complete response. Consolidation with high dose chemotherapy with autologous support was not feasible this time because of poor mobilization of progenitor cells, so the patient was put on surveillance.

Two years later, in 2009, the patient had a third relapse of the disease manifested as a left scapular region plasmacytoma treated with local radiotherapy with a total of 37.5Gy with good response. She was maintained on Prednisolone 60mg/day. One month later she was admitted to the hospital with marked fatigue, loss of weight, jaundice and abdominal pain. The hematologic tests revealed anemia (Hb<7.6 g/dL) and thrombocytopenia (platelet count 11x10⁹/L), high serum lactate dehydrogenase (2860U/L, normal range 240-480U/L)
and abnormalities of liver function tests (GGT - 3635U/L, normal range 10-66U/L; alkaline phosphatase - 840U/L, normal range 39-117 U/L; AST - 225U/L, normal range 0-37U/L; ALT - 345U/L, normal range 0-41U/L; bilirubin 7mg/dL, normal range 0-1mg/dL) without stigmata of chronic liver disease. There was no hypercalcemia or renal insufficiency. The bone marrow did not show infiltration with plasma cells and serum and urine immunofixation were also negative. However, the free light chain assay ratio was abnormal. Abdominal ultrasound revealed multiple space occupying lesions which were corroborated by CT scan (Fig.1). A transjugular hepatic biopsy of the lesions was done. The histology and immunohistochemical study of the lesions were compatible with hepatic plasmacytoma (Fig.2). The clinical situation deteriorated with worsening of the cholestatic hepatitis (bilirubin 35mg/dL). The patient became comatose and died a month later.

![Fig 1. Abdominal CT scan showing multiple space occupying lesions.](image)

**Discussion**

Nonsecretory multiple myeloma (NSMM) is a rare variant of multiple myeloma and has been associated with a variety of clinical features but in contrast to conventional multiple myeloma it is generally devoided of terminal organ damage, hypercalcemia and lytic bone lesions [4]. However, other reports showed that skeletal radiographic surveys always revealed lytic lesions with fractures and bone pain [5]. Normocytic normochromic anemia and thrombocytopenia are usually present. Hypogammaglobulinemia has frequently been described and may be a sign of defective immunoglobulin production. Bone marrow infiltration with plasma cells is usually between 20% and 75%. The non-secretors survive significantly longer than the secretors and this is thought to be due to earlier presentation possibly as a result of a tendency to form symptomatic local tumours [6]. However, in many occasions, due to the lack of physical findings, a delay in diagnosis of 1 to 12 months can occur. Our patient did have a course of disease oscillating between systemic disease and symptomatic local tumours. More recently, the disease relapsed as symptomatic multiple extramedullary liver plasmacytomas without systemic involvement or marrow plasmacytosis.

![Fig 2. Immunohistochemical staining of a biopsy specimen of a liver nodular lesion showing atypical plasma cells (x400).](image)

Myeloma may affect the liver through direct malignant diffuse cell infiltration, or it may present as a single or multiple space occupying lesions as plasmacytomas with extrahepatic biliary obstruction, ascites, nonobstructive jaundice and hepatomegaly [7]. Diffuse hepatic infiltration occurs in more than 50% of post-mortem cases. However, the nodular form as multiple extramedullary plasmacytomas, as in the case reported here, is a clinical rarity.

Although abnormalities in liver function tests and extensive plasma cell infiltration of the liver are common findings in MM, they are usually clinically silent and only rare cases of MM present as acute liver disease [8]. Our patient presented with abdominal pain, jaundice, pruritus and abnormal liver tests resembling an acute cholestatic hepatitis that was rapidly fatal.
Conventional treatment of the two forms of myeloma includes chemoradiotherapy, steroids, and in selected cases high-dose chemotherapy and hematopoietic stem cell transplantation to improve progression-free survival and overall survival. Novel anti-myeloma drugs such as immunomodulatory drugs IMiDS (Thalidomide) and proteosome inhibitors (Bortezomib) are nowadays used as upfront treatment of MM and in the relapsed disease.

Some reports showed extramedullary relapse of MM after treatment with thalidomide, with one case occurring as liver plasmacytoma [9]. It is known that thalidomide increases the expression of cytoadhesion molecules in myeloma cells and in the bone marrow microenvironment. Therefore it was suggested that some patients with multiple myeloma who relapse after thalidomide treatment may present with extramedullary plasmacytomas in the absence of progression of their disease in the bone marrow with the disease responding to proteosome inhibitors [9, 10]. Our patient presented extramedullary hepatic plasmacytoma as a relapse of NSMM after thalidomide and also bortezomib, thus pointing out to a multi-drug resistant disease.

This case illustrates the clinical aggressiveness of a non-secretory multiple myeloma relapsing after multiple therapeutic regimens including conventional chemotherapy, high dose chemotherapy with autologous stem cell transplantation and the more potent novel anti-myeloma agents. It underscores and confirms that nodular infiltration as hepatic plasmacytomas is a manifestation associated with an end-stage disease with a very poor prognosis and for which new therapeutic options are needed.

Non-secretory multiple myeloma and extramedullary hepatic plasmacytoma are both rare entities and as far as we know, this is the first report of a truly non-secretory multiple myeloma of the producer type relapsing as multiple extramedullary hepatic plasmacytomas associated with a fatal acute cholestatic hepatitis.

Conflicts of interest
The authors declare no potential conflicts of interest.

Authors’ contribution
RL cared for the patient, researched the topic, wrote/organized and reviewed the manuscript. AM and JV cared for the patient and reviewed the manuscript.

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References