Extramedullary Plasmacytoma of the Lung – Rather a Disseminated than a Localized Disease? – A Case Report of a Primary Pulmonary Plasmacytoma Showing Distinct Signs of Systemic Spread

Lisa Billecke[1], Eva Maria Murga Penas[1], Jozef Zustin[2], Thorsten Derlin[3], Carsten Bokemeyer[1] and Georgia Schilling*[,1]

[1]*Department of Oncology, Hematology, BMT with section Pneumology, Hubertus Wald Tumorzentrum – University Cancer Center Hamburg (UCCH), University Medical Center Hamburg Eppendorf (UKE), 20246 Hamburg, Germany*

[2]*Institute of Pathology, University Medical Center Hamburg Eppendorf (UKE), 20246 Hamburg, Germany*

[3]*Department of Nuclear Medicine, University Medical Center Hamburg Eppendorf (UKE), 20246 Hamburg, Germany*

Abstract: *Objective*: We report an unusual case of a patient with a plasma cell tumor presenting first as a primary pulmonary plasmacytoma (PPP) but then showing distinct signs of systemic spread.

Case Summary: A 58-year-old woman presented with an extramedullary plasma cell tumor of the lung with additional affection of lymph nodes above and underneath the diaphragm, without apparent infiltration of the bone marrow by malignant plasma cells, but with evidence of a small proportion of clonal plasma cells in FACS analysis. Due to the fact that the patient showed excretion of lambda light chains in the urine in addition to the solid manifestations on multiple sites and minimal bone marrow involvement, we verified the systemic spread. This is in contrast to primary extramedullary plasmacytoma presenting as solitaire plasma cell tumors mostly occurring in the upper aerodigestive tract or extramedullary myeloma, which describes relapses or extramedullary progression of multiple myeloma emerging in various organs. We herein present all features of a, to our opinion, systemic disease by means of affection pattern, laboratory values, and bone marrow infiltration.

Conclusion: This unusual case demonstrates the presentation of an extramedullary plasma cell tumor that appeared as a PPP but showed distinct signs of dissemination as well as uncommon features such as a monoclonal component of IgM type. This example reveales that extramedullary manifestations of plasma cell dyscrasia should be surveyed carefully as they can conceal an underlying systemic disease.

Keywords: Primary pulmonary plasmacytoma, extramedullary plasmacytoma, multiple myeloma, cytogenetics.

INTRODUCTION

Extramedullary plasmacytomas (EMP) are defined as isolated and localized extraosseus plasma cell tumors without bone or bone marrow involvement and without any signs of systemic spread. EMPs are predominantly (> 80%) located in the upper aerodigestive tract (UAD) and account for about 4% of all plasma cell disorders. They generally pursue an indolent clinical course with tendency for local recurrence and may rarely convert to multiple myeloma (MM). EMPs usually respond excellent to local therapies such as surgery or radiotherapy [1, 2].

In contrast, secondary extramedullary relapses of MM in solid organs (EM), often occurring as late events and dissemination in disease progression, indicate an aggressive disease and often herald a poor prognosis [3]. Until now, to our best knowledge, extramedullary manifestations of plasma cell tumors described in the literature, including primary pulmonary plasmacytoma (PPP), have been allocated either to EMPs or to EM relapses and were treated predominantly with local therapies when thought to belong to the EMP group or systemic therapy in case of EM relapse of a MM. However, it has been suggested previously that a PPP may not always be localized and that, when examined more carefully, may show signs of systemic spread [4]. Sensitive imaging techniques such as computed tomography (CT) and magnetic resonance tomography (MRT), and immunological and histopathological investigations play an important role in the diagnostic procedure of PPP and help to differentiate between a localized or an already disseminated disorder. We describe in this case report the clinical course and all relevant laboratory findings, including cytogenetics, of a plasma cell tumor presenting first as a pulmonary

*Address corresponding to this author at the Department of Hematology and Oncology, BMT with section of Pneumology, Hubertus Wald Tumorzentrum - University Cancer Center Hamburg (UCCH), University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburg, Germany; Tel: +49 40 7410 55692; Fax: +49 40 74105 6744; E-mail: g.schilling@uke.de

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plasmacytoma but then showing signs of systemic spread.

CASE REPORT

A 58-year-old caucasian female was admitted to hospital, suffering from increasing exertional dyspnea and cough without further symptoms as night sweats, fever, or weight loss. Physical examination revealed no significant abnormalities. Ultrasound and chest X-ray detected a pleural effusion in the right lung. The pleura aspirate showed signs of chronical inflammation, but no malignant cells. Bronchoscopy indicated a distinct chronical tracheobronchitis without any presence of pathological cells. CT scans revealed a small mass in the middle lobe of the right lung, which was subsequently biopsied (Figure **1A**).

Histopathological and Immunohistochemical Findings

The histopathological investigation of the biopsy revealed dominance of plasma cells with nuclear inclusions and characteristic cytoplasm (Figure **2A**). The plasma cells expressed CD38 (Figure **2B**) and CD138, and showed lambda light chain restriction without co-expression of CD56 (Figure **2C**). As a consequence of the uncommon presentation, a second independent histopathological analysis was performed, confirming the previous findings and additionally revealing the expression of CD20 in 70% of plasma cells (Figure **2D**).

Laboratory Values

Serum immunofixation revealed a monoclonal IgM lambda gammopathy. Other relevant laboratory values were as follows: clear elevation of serum lambda free light chains: 559.10 mg/L (5.71–26.30) (FLC), κ/λ-ratio of 0.02 (0.26–1.65), β2 microglobulin: 2.37 mg/L (0.8–2.2), and a considerably high IgM: 9.34 g/L (0.40–2.30). 24 h-urine revealed a significantly increased lambda light chain excretion of 288.20 mg/24 h (-4.20). Bilirubin was 1.9 mg/dL (–1,0), glutamate pyruvate transaminase (GPT) 200 U/l (10-35), and glutamate oxalate transaminase (GOT) 106 U/l (10-35). Blood cell counts were normal, as well as creatinine, lactatdehydrogenase (LDH), total protein, albumin, and C-reactive protein (CRP). Bone marrow aspiration showed no significant infiltration of plasma cells in the cytomorphological survey.

FACS Analysis and FDG-PET/CT

Fluorescence-activated cell sorting (FACS) analysis of the bone marrow aspirate revealed a minimal

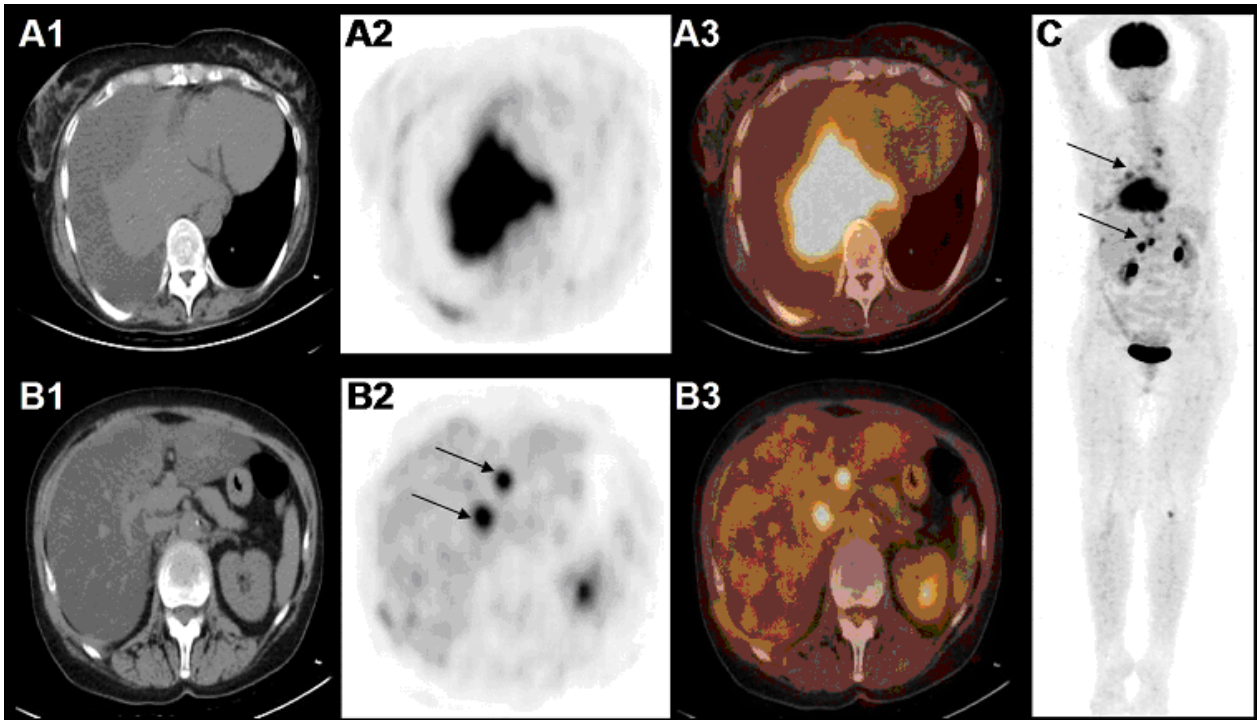

Figure 1: Transverse PET/CT images demonstrate supradiaphragmal (**A1/2/3**) and infradiaphragmal (**B1/2/3**) metabolic activity (arrows in **B2** point to metabolic active lymph nodes infradiaphragmal). Whole-body maximum intensity projection (MIP) PET image shows metabolically active manifestations in the right lung (arrow), in the mediastinum, and in portal lymph nodes (**1C**, arrow).

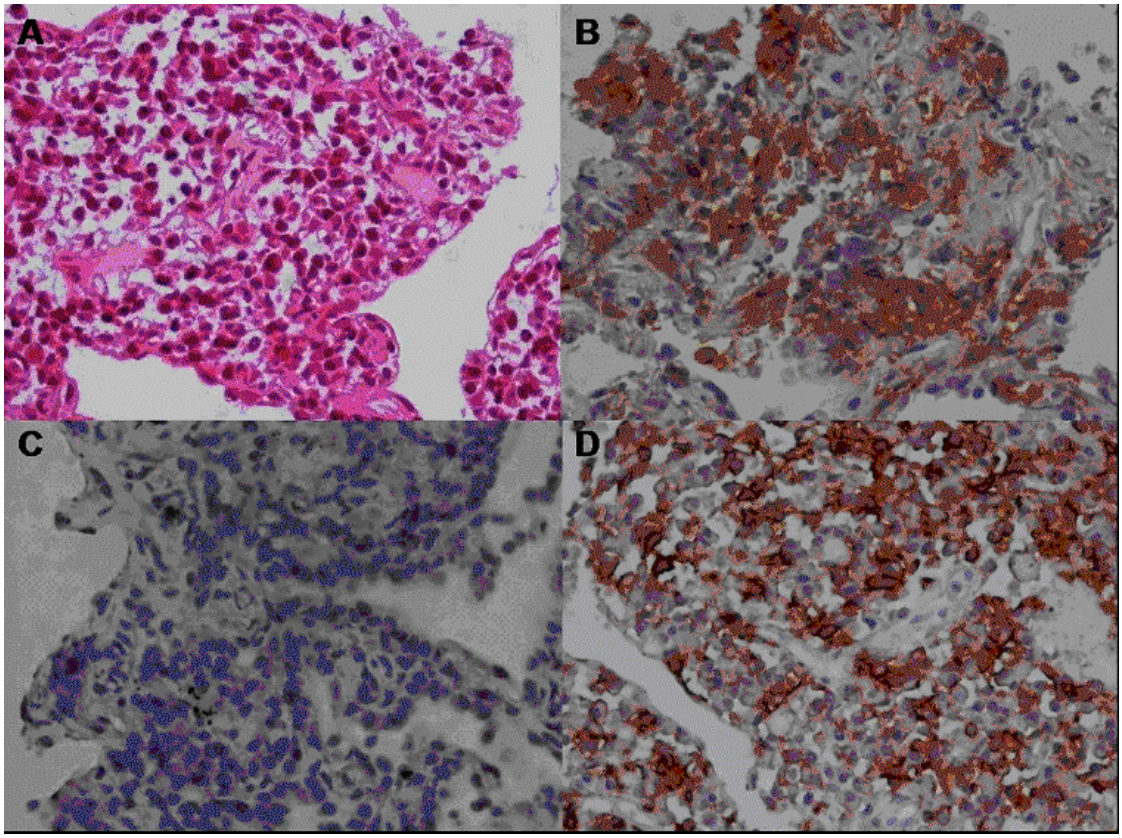

Figure 2: Hematoxylin staining of the biopsy reveals plasma cells with enlarged nuclei and characteristic cytoplasm (**A**). Immunohistochemistry shows strong positivity for CD38 (**B**), negativity for CD56 (**C**), and positivity for CD20 (**D**) (40x).

infiltration of plasma cells negative for CD45 and with aberrant expression of CD56 together with strong expression of CD38 and CD138. 18F-fluorodeoxyglucose positron emission tomography/ computed tomography (FDG-PET/CT) scans demonstrated tracer accumulation on both sides of the diaphragm, not only in regional lymph nodes as described in other cases (Figure **1**).

Cytogenetics

For cytogenetic investigation of the paraffin-embedded lung biopsy probe, we combined fluorescence *in situ* hybridization with a staining of intracytoplasmatic light-chains (κ or λ) using fluorescently labeled antibodies (cIg-FISH). Results revealed no abnormalities of *TP53* (17p13), *C-MYC* (8q24), and D13S25 (13q14), but detected the translocation t(4;14)(p16.3;q32) that is unfavorable for prognosis.

Treatment

Taken all findings together, we considered an extramedullary PPP type IgM lambda in the context of an already disseminated disorder. Consequently, a systemic therapy analogous to standard MM treatment with induction therapy (bortezomib, cyclophosphamide, and dexamethason) followed by high-dose chemotherapy and autologous stem cell transplantation was initiated.

After these first three courses we could demonstrate a near complete remission with normalized laboratory values but still positive serum immunofixation: IgM 1.56 g/L, lambda light chains 21.63 mg/L, *β*2 microglobulin 2.0 mg/L, GOT 63 U/L, GPT 34 U/L and bilirubin 0.6 mg/dL. The follow-up PET-CT scan could not detect remaining metabolically active manifestations. Due to a septic complication with multi-organ failure, the patient died after stem cell mobilization therapy. Post mortem autopsy detected no atypic plasma cell infiltration in the lungs, lymph nodes, bone marrow, or any other organ, which implies a complete pathological remission.

DISCUSSION

All extramedullary manifestations of plasma cells described in the literature so far have been assigned to the group of EMP or to extramedullary relapses of MM. EMPs are defined as isolated extraosseus plasma cell tumors, occurring in any organ or tissue, without bone

marrow infiltration or signs for systemic spread. Small amounts of M-protein as described in any cases do not imply exclusion of a locally limited disease [1]. EMPs are characterized by an indolent clinical course, with a tendency towards local recurrence, and only sporadically progress to MM. Pulmonary or pleural EMPs, which were first reported by Gordon and Walker, are very rare [5]. Laso and coworkers already considered EMP to be a systemic disease, rather than a local tumor, based on the identical DNA index in both the plasma cells from the bone marrow and the extramedullary mass [4].

In a literature survey comprising 869 patients with EMPs, only 15 cases showed an affection of the lung [2]. In addition, less than 50 cases of PPP have been published so far [6, 7]. An analysis of the early literature is difficult due to the different diagnostic criteria for EMP until 2004, when a consensus definition was established [8]. The overall 2- and 5-year survival rates of PPP are 66% and 40%, respectively. A recent study with 19 cases of PPP reported a long-term survival of two patients surviving for 20 years or more [9]. Conversely, in another study, 9 out of 22 (40%) reported PPP cases progressed early to MM suggesting an underlying, not recognized, disseminated disease already at the time of diagnosis [7]. When progressing to MM, survival rates are similar to that of other patients with MM.

In contrast to these findings, secondary EMs in solid organs occur as late events in disease progression of MM, frequently after intensive treatment modalities as autologous or allogeneic stem cell transplantation. They indicate an aggressive disease and often herald a poor prognosis [3, 10]. Pulmonary involvement in secondary EM is a very rare event. In a study of 958 patients with MM, 10% had pulmonary affection, but only one case showed histologically proven plasma cell involvement [11].

Diagnostic procedures for differentiation between a systemic and a localized pulmonary plasmacytoma should include sensitive imaging techniques (such as CT and/or MRT) and a complete endoscopic examination, bone marrow and tumor biopsies, serum electrophoresis, immunohistochemistry, immunoglobulin quantification, immunoelectrophoresis or immunofixation of urine and serum, and a *ß2* microglobulin assay. For localized PPP, chemical laboratory findings are normal although a small M-component may sometimes be present. The occurrence of specific elevated laboratory parameters, such as *β*2 microglobulin, monoclonal IgM paraprotein and free light chains in serum, as well as urine excretion of lambda light chains are suggestive of a systemic disease. Additionally, the affection of multiple sites as seen in our case – although not biopsy proven – can be verified by PET-CT imaging. General recommendations for treatment of PPP include chemotherapy in cases of multifocal occurrence, radiation therapy, and/or surgical resection [12, 13, 14]. In cases of disease dissemination, systemic therapy approaches such as high dose chemotherapy and autologous stem cell transplantation are indicated. It is important for clinicians to recognize the possibility of a systemic spread and to analyze this disease carefully by means of affection patterns, laboratory values, and bone marrow involvement in order to select an optimal therapy concept.

Cytogenetic analyses have an important prognostic value in patients with MM, helping to identify high-risk patients. One genetic alteration expected to be associated with extramedullary progression of MM is deletion of 17p13 [15]. This genetic aberration has been correlated with poor prognosis and resistance to chemotherapy in MM [16, 17]. 17p13 deletion was not detected in our case. The only aberration we found by cIg-FISH was translocation t(4;14) involving the *IgH* locus and *FGFR3/MMSET*, known to be a primary event in MM and of unfavorable prognosis. However, the patient showed a very good response to the first courses of conventional chemotherapy but of course follow-up was too short to reveal evidence with respect to the true prognosis.

Morphologic and phenotypic criteria of extramedullary plasma cell tumors are rare. Focussing on CD56 (NCAM), results differ and are discussed controversially [18, 19, 20]. Downregulation of CD56 is thought to be associated with a more aggressive disease and dissemination of myeloma cells to extramedullary sites, as it is seen e.g. in plasma cell leukemia and confirmed in our case [19]. In addition to the unusual site, the EM in our case showed uncommon features such as IgM subtype. The majority of intact immunoglobulin MM has a monoclonal component of IgG or IgA type. IgM myeloma is a very rare disease accounting for approximately 0,5% of all MMs [21]. Diagnosis of Waldenström´s macroglobulinaemia (WM) is by contrast considerably more frequent [22].

CONCLUSION

Taken together we found clearly elevated laboratory parameters, such as *β*2 microglobulin, monoclonal serum paraprotein (IgM subtype), and detection of free light chains in serum, as well as urine excretion of lambda light chains, involvement of multiple lymph nodes on both sides of the diaphragm additional to the pulmonary mass and minimal bone marrow involvement. These findings lead to the diagnosis of a systemic disease, which should rather be named primary pulmonary myeloma than PPP to satisfy the criteria of dissemination. In conclusion, we propose that extramedullary manifestations in plasma cell dyscrasia must be surveyed carefully to not miss a systemic underlying disease.

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