CASE REPORT

Myelomatous Meningitis - a diagnostic and therapeutic challenge

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ABSTRACT

Multiple myeloma is a malignant disease, which consists of the clonal proliferation of plasma cells that will lead to the accumulation of a monoclonal protein in the serum and/or urine, with organic damage. Extramedullary involvement is found in approximately 5% of cases of myeloma.

Multiple myeloma with determination in the central nervous system is extremely rare and is associated with a bad prognosis.

A targeted treatment scheme for this complication is not described, but the therapeutic approach should follow the same steps as in the case of other lymphoproliferative diseases with neurological involvement (association of intrathecal chemotherapy applications - cytarabine and methotrexate, with systemic treatment and depending on the response local radiotherapy should be performed).

The occurrence of extramedullary disease in the evolution of multiple myeloma is a complication associated with a poor prognosis.

CNS – Central Nervous System; CSF- Cerebrospinal fluid; CyBorD- cyclophosphamide, bortezomib, dexamethasone; CR- complete response; KRD- carfilzomib, lenalidomide, dexamethasone; NSTEMI- Non-ST-Elevation Myocardial Infarction; TIA- transient ischemic attack

Introduction

Multiple myeloma is a hematological malignancy, characterized by the clonal proliferation of plasma cells that will lead to the accumulation of a monoclonal protein in the serum and/or urine, with organic damage. It represents 1% of all malignant diseases and 10% of hematological ones. In its classic form of presentation, the bone marrow represents the seat of plasma cell proliferation, but extramedullary infiltration can affect any or-pleura, central nervous system)[3]. Extramedullary involvement appears in approximately 5% of cases of multiple myeloma and can occur either through hematogenous dissemination of malignant cells[1,2] or through contiguity from the bone cortex. In recent years, the incidence of the extramedullary disease has increased. The reason for this is, probably, the improved survival of patients with multiple myeloma, due to the introduction of innovative therapies. Extramedullary disease in multiple myeloma must be differentiated from solitary plasmacytoma, which is a different entity, with distinct evolution, prognosis, and treatment.

Multiple myeloma with central nervous system involvement is extremely rare and it is associated with a poor prognosis, with reported median overall survival from diagnosis of only seven months[4] or less. Infiltration of the central nervous system in multiple myeloma is characterized by the presence of monoclonal plasmacytic infiltrate either at the CNS level or at the meningeal level. This complication occurs in less than 1% of all patients with multiple myeloma. In exceptional cases, it can appear right after diagnosis, but it is more common in patients with refractory/relapsed disease. Diagnosing myelomatous meningitis can be extremely difficult, considering the low frequency of cases and the heterogeneity of symptoms. Clinical manifestations can be easily confused with neurological symptoms caused by the pathology itself (hypercalcemia, uremia, or hyperviscosity), or which appear secondary to the treatment. The clinical presentation of a patient with myelomatous meningitis consists of visual disturbances, motor or sensory deficit, headache, radicular pain, confusion, bradylalia, bradypsychia, and, less often, convulsions, vertigo, hearing disorders, high fever, cranial nerve paralysis or lethargy may occur. In order to confirm the diagnosis, a morphological exam should be performed. This will detect atypical plasma cells at the site of the central nervous system (cerebrospinal fluid). After that, the flow cytometry exam will highlight the presence of CD 38/CD 1388. Also, the detection of a monoclonal protein at the site of the cerebrospinal fluid indicates a myelomatous determination at this level. Due to the small number of diagnosed cases, not many studies related to this complication have been performed, and the data available in the literature are few. However, some characteristics are well known: among the types of immunoglobulins, Ig A is most frequently associated with neurological determination, and lambda is more often implicated in myelomatous meningitis.[4] The cytogenetic risk analysis highlighted the fact that the most frequent chromosomal abnormality encountered in patients with multiple myeloma and myelomatous meningitis was del (13q)- 39%, followed by the presence of del (17p)- 23%.4 A targeted treatment scheme for this complication is not described, but the therapeutic approach should follow the same steps as in the case of neurological determination in other lymphoproliferative diseases. The scheme used for treatment must associate intrathecal chemotherapy applications (cytarabine and methotrexate) with systemic treatment and, depending on

the response, craniospinal radiotherapy should be performed. Choosing systemic treatment in this situation can represent a real challenge, both from the perspective of the fact that it is a complication that occurs rather in patients with refractory disease and who have already been exposed to several therapeutic lines and because of the fact that drugs must penetrate the bloo-brain barrier. Among the drugs used in the systemic treatment of multiple myeloma, proteasome inhibitors (bortezomib, carfilzomib, ixazomib), with the exception of marizomib[9,10], do not cross the blood-brain barrier. Immunomodulators (thalidomide, lenalidomide and pomalidomide) and high doses of steroids have this property[6]. Considering modern therapies, monoclonal antibodies are of great interest. It has been demonstrated that daratumumab (monoclonal antibody against CD 38) can cross the blood-brain barrier7, and this is the reason why it must be included in the systemic treatment schemes for patients with multiple myeloma and central nervous system determination. Due to the sensitivity of clonal plasma cells to radiotherapy, this is often used in the treatment of multiple myeloma and solitary plasmacytomas. The association of craniospinal radiotherapy in the treatment of myelomatous meningitis improved survival[1].

Clinical case

We report a case of a 68-year-old patient with a history of Multiple Myeloma IgA kappa std R-ISS 2 and L1 paravertebral plasmacytoma, diagnosed in November 2018, in the Hematology Department of the Fundeni Clinical Institute. The patient received 6 cycles of CyBorD, followed by consolidation with bone marrow autotransplantation (April 2019) and radiotherapy at the T10 - L3 level. He achieved CR response after first-line treatment. 16 months after the autotransplantation was performed disease progression is detected. We decided to start KRD treatment with weekly Carfilzomib administration. After two cycles of treatment complete response was achieved. During the treatment, grade II hiccups and grade II hoarseness appeared, and the dexamethasone dose was reduced from 40 mg per week to 20 mg per week and then to 12 mg per week.

In March 2021 (during the 6th cycle of treatment) suddenly appear bradylalia, radypsychia, and amnesia. A neurological evaluation was carried out, with a Doppler ultrasound evaluation of the carotid arteries (normal Doppler flow, without stenoses), and a cerebral CT scan (without acute intracerebral lesions) was performed. The diagnosis of TIA was established, and for the patient's safety, we decided to temporarily stop the medication and monitor the patient for 21 days. Throughout this period, the complete response to the treatment is maintained. During the ninth KRD cycle (June 2021), anterior chest pain appears.The EKG examination performed revealed repolarization changes in the lateral territory. Later, the patient was admitted to the hospital, and the investigations performed showed: troponin is with positive dynamics, the kinetic disorder of the lateral wall, without affecting the overall systolic function of the left ventricle (transthoracic ultrasound), and unicoronary lesion (coronary angiography performed 3 days after the anginal episode). The diagnosis of NSTEMI was established and angioplasty with an active pharmacological stent was performed. Considering the cardiological event as an adverse event related to the administration of Carfilzomib, it was decided to continue the treatment only with Lenalidomide and Dexamethasone, starting with cycle10. Until the end of the treament, complete response was maintained. Considering the response totreatent, the patient

was evaluated at 3 month intervals, until Marc 2022, when he was admitted in emergency, to another hospital unit, complaining of severe occipital headache and visual disturbances (horizontal diplopia and blurred vision). The ophthalmological examination revealed papillary edema, and the cerebral CT scan: multiple pseudo nodular images visible in both cerebral hemispheres, the largest of 35/17 mm located temporoinsular on the right side with the appearance of secondary determinations.

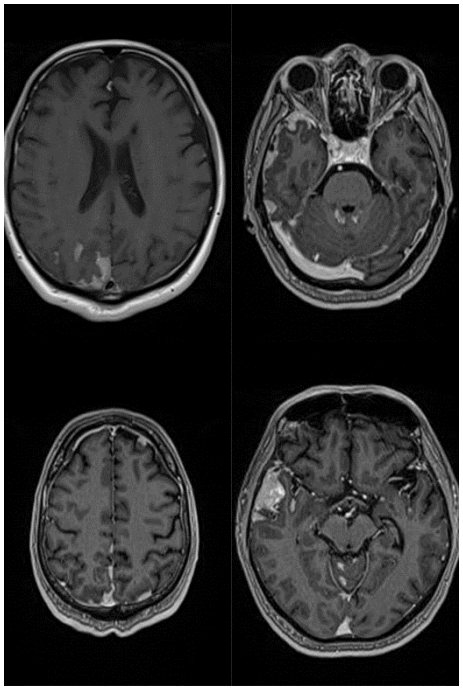

Figure 1. MRI at diagnosis showed multiple lesions structured nodular and in plaques with a tumor appearance, localized predom inantly leptomeningeal as well as capsulo-len ticular on the right side, and which associate mass effect on the right anterior temporal pole. The evaluation of the smear from the cerebrospinal fluid sediment revealed cellu larity consisting of frequent plasma cells. Im munofixation of the cerebrospinal fluid revealed the IgA lambda compact band.

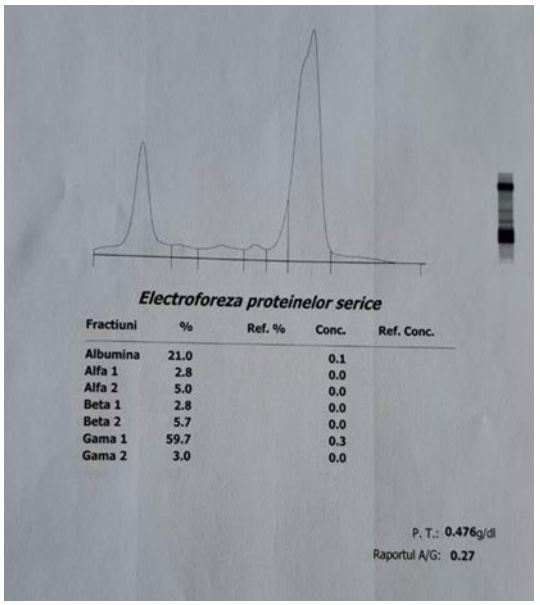

Figure 2. CSF electrophoresis

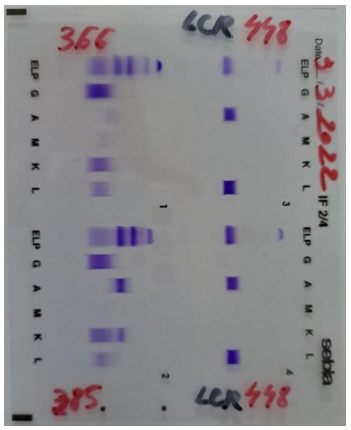

Figure 3. CSF Immunofixation

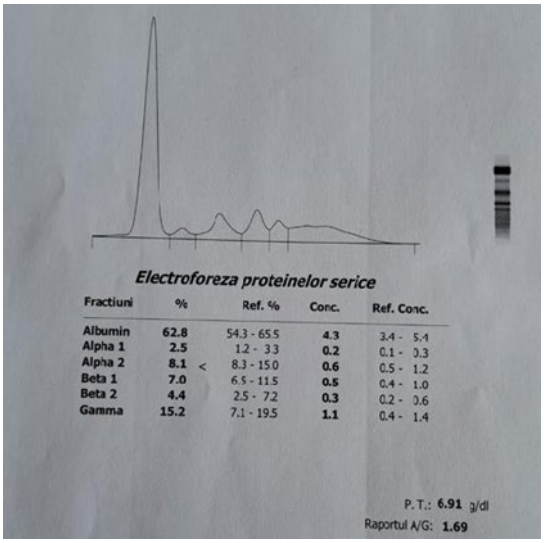

Figure 4. Serum electrophoresis Blood tests were also performed at that time: serum electrophoresis: SPEP 0 g/dl; Ig A 3.3 g/l; free lambda 131 mg/l; SFLC ratio 7.7; SFLC difference 114. The bone marrow examination revealed only 8 % plasma cells and the FISH exam was with standard risk. The diagnosis of myelomatous meningitis was established and treatment was started. Systemic therapy with Dara-tumumab (1800 mg, weekly), Pomalid-omide (4 mg per day, for 21 days), and Dexamethasone (20 mg weekly) to which intrathecal administration of Methotrexate (15 mg), Cytarabine (40 mg) and Dexamethasone (20 mg) was associated. The subsequent evolution was favorable. From the clinical point of view, there was a rapid remission of neurological symptoms shortly after the initiation of treatment, and from the biological point of view there was a decrease in proteinorrhagia from 4760 mg/l to 596 mg/l, and the disappear-ance of plasma cells from the CSF. The brain MRI exam performed in June 2022 showed a clear regression, both numerical and dimensional, of the previously described meningeal determinations.

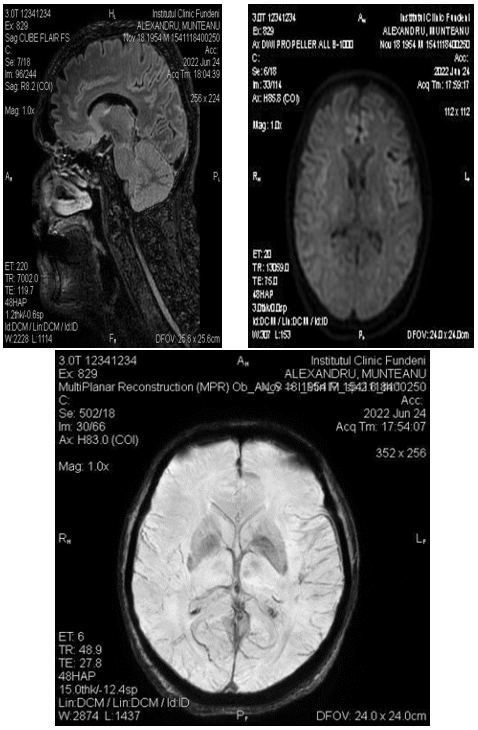

Figure 5. MRI performed after treatment shows disease regression. Until now, (6 months after the diag-nosis of myelomatous meningitis), the patient has a partial remission of the disease, with the remission of neurological symptoms and good quality of life. Six intrathecal appli-cations, five courses of Daratu-mumab-Pomalidomide-Dexame-thasone, and craniospinal radiotherapy were performed, without major complica-tions secondary to treat-ment administration. Although the evolution of the disease is not long, only 4 years until now, the complica-tions, both related to the treatment and the disease, were multiple, posing important problems in the management of the case.

Conclusions

The occurrence of extramedullary disease in the evolution of multiple myeoma

is a complication associated with a poor prognosis. The extramedullary determination at the central nervous system, although it occurs very rarely, it shows an increase in incidence in the last period. A possible explanation for this aspect is the improvement of overall survival in patients with multiple myeloma, which favors the appearance of new mutations in tumor cells that were resistant to treatment.5 Currently, myelomatous meningitis gives a gloomy perspective to the patient's evolution and requires a fast and innovative therapeutic approach. Improving the understanding of this complication will allow us to identify highris cases of multiple myeloma with central nervous system involvement, and this will lead to a different approach to the case.

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