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Clinical Reports

Meningeal infiltration by non-myelomatous IgD-secreting plasma cell dyscrasias

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Summary: Two cases of meningeal invasion by non-myelomatous plasma cell dyscrasias – a plasma cell leukaemia and an extramedullary plasmacytoma – are described. Both were secretors of IgD paraprotein and both were diagnosed in life, characteristics which we have not found in any other published case of plasma cell leptomeningitis. Analysis of our patients and of another 25 cases suggests as predisposing factors of meningeal invasion the male sex, presentation in the form of plasma cell leukaemia, presence of the IgD paraprotein and tumoral involvement of pleura, lung, pericardium and testicles.

Aggressive treatment of this neurological complication controlled the meningeal disorder in some cases. However, the majority died of disseminated disease in spite of systemic chemotherapy. Until an effective treatment can be found, able to maintain remission or cure the systemic disease, prophylaxis of the central nervous system in plasma cell dyscrasias does not appear to be advisable.

Introduction

The malignant proliferation of plasma cells may appear in a generalized form as multiple myeloma and plasma cell leukaemia, or in a localized form as solitary bone plasmacytoma or extramedullary plasmacytoma. The diagnostic criteria and clinical, analytical and prognostic-therapeutic characteristics of the different types have been described.[1,2]

Diffuse meningeal involvement is a very rare complication with only isolated published examples. The majority of cases are due to multiple myeloma with IgG or IgA paraprotein. We present two cases of non-myelomatous IgD plasma cell dyscrasias with meningeal involvement which were diagnosed in life, a previously unreported event.

Case reports

Case 1

A 47 year old male presented in May 1980 with diplopia, retroorbital pain and left ptosis for one month. Palsies of the left cranial nerves III and IV and left papillary oedema were noted. Computerized tomography (CT) scan and carotid angiography revealed a hyperdense mass in the left cavernous sinus invading the sella turcica and the orbital vertex, and displacing the carotid artery anteriorly (Figure 1). Craniotomy revealed a parasellar extradural tumour, the biopsy of which led to a diagnosis of pituitary adenoma. Fifteen days later, another examination

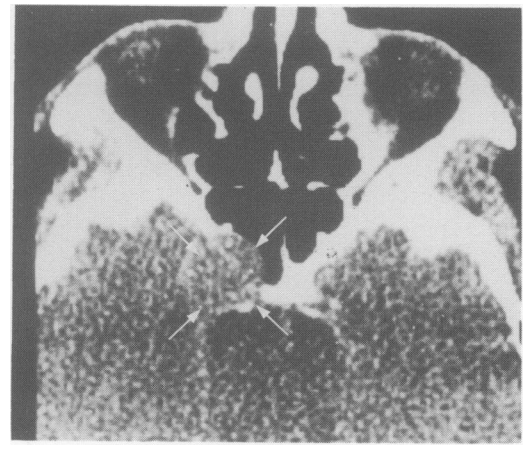

Figure 1 CT scan. A mass can be observed, located in the left cavernous sinus and invading the sella turcica (arrows).

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disclosed two subcutaneous nodules in the occipital and left hemithorax regions and enlarged cervical and inguinal lymph glands. The patient's left knee was stiff and enlarged. The haemogram was normal except for an erythrocyte sedimentation rate (ESR) of 76 mm in the first hour. Urine, and blood biochemical analysis were normal. X-rays of thorax, abdomen and rib cage were normal, but in the distal third of the femur there was cortical destruction and enlargement of soft tissues. A biopsy of the occipital nodule was histologically identical to that of the intracranial mass. Material from one of the enlarged glands revealed atypical plasma cells. Owing to this finding, the two previous biopsies were reviewed, and in both, the diagnosis of plasmacytoma was confirmed. Serum and urine electrophoresis were normal. Immunoelectrophoresis detected an IgDλ paraprotein in serum and λ light chains in urine. Immunoglobulin levels were: IgG, 704 mg/dl; IgA, 169 mg/dl; IgM, 24 mg/dl; and IgD, 31 mg/dl. Lumbar puncture revealed normal biochemistry, cytology and electrophoresis; paraprotein was not detected. Two bone marrow biopsies showed no signs of myelomatous invasion.

With the diagnosis of disseminated EMP, in May of 1980, chemotherapy with vincristine, melphalan, cyclophosphamide and prednisone was begun, resulting in remission of clinical and laboratory findings. In June of 1981, one month after the discontinuation of treatment, tumour recurred in a testicle and was controlled by means of local radiotherapy. In mid-August 1981, multiple subcutaneous and ganglionic plasmacytomas appeared, and a radiograph of thorax revealed pericardial effusion and pulmonary interstitial pattern. The serum IgD was 300 mg dl. Polychemotherapy was renewed according to the M_2 protocol (vincristine, cyclophosphamide, BCNU, melphalan and prednisone), resulting in spectacular but short-lived remissions, with new tumoral growths appearing between cycles. In October, the patient had radiating pain in the lumbar region and lower left limb with paresis of both lower limbs. A few days later, he was admitted with temporospatial disorientation without focal neurological signs. Radiography of thorax was normal and brain CT scan demonstrated the existence of discrete lesions in the sella turcica, with no change with respect to the initial remission. Examination of the cerebrospinal fluid (CSF) revealed 0.38 mmol/l glucose, 112 mg/dl proteins, and 5×10^6 cells/l, the majority of them plasma cells. Electrophoresis of the CSF was normal and the IgD level was 15 mg/dl. The patient's haemogram showed pancytopenia with no evidence of plasma cells, and the bone marrow remained free of myelomatous invasion. Halfbody radiotherapy of the upper hemibody and sacral region and intrathecal methotrexate treatment were commenced, resulting in normalization of the CSF. Subsequently, the patient developed fever with very profound pancytopenia, and died in December of 1981. Necropsy was not authorized. Prior to the presentation of meningeal infiltration, this patient had been reported as a case of pituitary adenoma-like intracranial plasmacytoma.[3]

Case 2

A 44 year old male began to suffer diplopia and left ptosis in March of 1981. In April, dorsal and lumbar pain developed, extending to the left lower limb. Soon after, nausea, vomiting and constipation appeared. The patient was asthenic, and has lost 5 kg of weight since the appearance of his symptoms. On physical examination, several subcutaneous nodules were observed on the head and chest, and there was involvement of left cranial nerves III, IV, V and VI and of the left S_1 nerve root. His haemoglobin was 6.5 g and leucocytes 13.4×10^9/l, 30% of which were plasma cells. ESR was 114 mm in the first hour. There was proteinuria of 2.3 g/l. Biochemistry revealed calcium 14.1 mg/dl, creatinine 3.8 mg/dl and a raised serum uric acid. Radiography and thoracic tomography revealed a parahilar mass at the level of the aortic arch, with erosion of D_4. CT scan showed mass in the sinus and the sphenoid cleft. Biopsy of a subcutaneous nodule gave a diagnosis of plasmacytoma. The bone marrow was invaded by poorly differentiated plasma cells which constituted 40% of the total cells. Serum electrophoresis showed hypogammaglobulinaemia, and a urinary monoclonal peak appeared in the γ region. There was an IgDλ monoclonal paraprotein and λ light chains, in the serum and urine respectively. The immunoglobulin levels were IgG, 480 mg/dl; IgA, 39 mg/dl; IgM, 28 mg/dl; and IgD, 680 mg/dl. The CSF showed glucose, 63 mg/dl; proteins, 152 mg/dl; cells, 6×10^6/l, all lymphocytes.

With the diagnosis of plasma cell leukaemia, polychemotherapy was initiated with melphalan, cyclophosphamide, vincristine and prednisone, resulting in clinical and laboratory parameter remission in the second cycle.

In September 1981, after receiving six cycles, the patient was admitted with involvement of the left cranial nerves II, III, IV, V, IX, X, XI and XII, left D_{10} root and cauda equina. Radiological study of spinal cord and cranium manifested no changes, and a myelography was normal. The brain CT scan demonstrated growth of the cranial mass. The CSF showed 60×10^6 cells/l, all of them poorly differentiated plasma cells (Figure 2). Immunoelectrophoresis detected IgDλ paraprotein. Blood and urine tests were normal. Chest X-ray showed mediastinal adenopathy and left pleural effusion which was shown to contain poorly differentiated plasma cells. Therapy combining cranial radiation, intrathecal methotrexate and

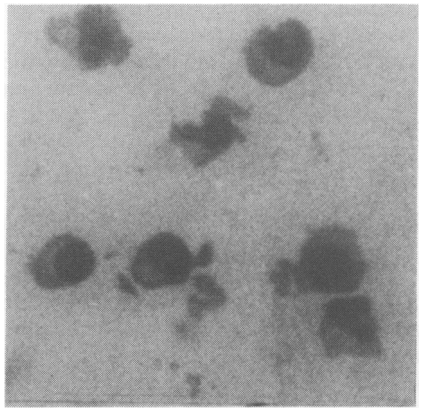

Figure 2 Atypical plasma cells in the cerebrospinal fluid. Giemsa staining (× 1000).

systemic polychemotherapy resulted in partial clinical remission and normalization of the CSF. The patient deteriorated progressively and died in December of 1981. Necropsy was not authorized.

Discussion

Diffuse meningeal metastasis is a serious neurological complication of certain neoplasms, among which should be included plasma cell dyscrasias. Prolongation of patient survival and the inaccessibility of the central nervous system to systemic chemotherapy are probably reasons for the increase in the incidence of neoplastic leptomeningitis. Three pathways of propagation have been suggested which, in practice, are difficult to differentiate: (a) direct, via tumoral masses subjacent to the leptomeninges; (b) neurogenic, by means of a paravertebral tumour propagated via the spinal nerves; and (c) haematogenous.[4] Regardless of the pathogenic mechanism, we have found 25 published cases, including our two, of plasma cell dyscrasias with meningeal involvement,[5-25] diagnosed on the basis of plasma cells in the CSF and compatible clinical data, criteria similar to those employed by Wasserstrom *et al.*[4] Another two cases have been diagnosed at necropsy.[26,27] The principal characteristics of these 27 patients are shown in Table I.

The mean age is 56 years, and males predominate over females at a ratio of 3/1. The most frequent type of dyscrasia is multiple myeloma, which was found in 18 individuals, whereas the non-myelomatous forms are found in three cases each. Two myeloma patients developed plasma cell leukaemia coinciding with the meningeal involvement. The predominant paraprotein detected in 10 patients is IgG, followed by IgA, IgD and Bence Jones, which are secreted in 8, 5 and 4 cases, respectively. Predominance of a determined light chain is not observed. The mean time between initial diagnosis of the plasma cell neoplasia and appearance of meningeal involvement is shorter among the generalized forms, myeloma and leukaemia, than in those that initially are localized (solitary bone and extramedullary plasmacytomas), although the difference is not statistically significant owing to the small number of patients.

All of the patients had plasma cells in CSF and clinical evidence of meningeal involvement. The existence of some plasma cells in the CSF in the absence of a compatible clinical picture should probably not be considered evidence of diffuse meningeal invasion, as suggested by the favourable evolution of some extradural plasmacytomas with a few malignant cells in the CSF when treated with local radiotherapy.[28] Cerebral signs and symptoms, especially stupor and headache, are the most frequent, followed by those derived from the spinal roots and the cranial nerves. In the majority of the cases, the

Table I Principal characteristics of 27 cases of plasma cell leptomeningitis, including the present two cases

Age (years): mean 56; range 37–73	
Sex (male/female): 20/6	
Paraprotein (no. of cases):	
IgG	10
IgA	8
IgD	5
BJ	4
κ/λ	11/9
Dyscrasia (no. of cases):	
Multiple myeloma	18†
Plasma cell leukaemia	5
Extramedullary plasmacytoma	3
Solitary bone plasmacytoma	3
Time of appearance of meningeal involvement (months): mean 12.5; range 0–60	
Clinical symptoms (positive cases/documented cases):	
– cerebral	21/25
– cranial nerves	8/25
– spinal nerves	11/25
Cerebrospinal fluid (positive cases/documented cases):	
Plasma cells	25/25
Paraprotein	13/14
Treatment (positive cases/documented cases):	
Intracranial radiotherapy	10/24
Intrathecal chemotherapy	16/24
Systemic chemotherapy	5/24
Survival (no. of cases):	
< 3 months	25
> 3 months	2

†2 cases evolved into plasma cell leukaemia.

extraneurological disorder was not controlled. The existence of 8 cases of plasma cell pleuropulmonary involvement is worthy of note. Paraprotein appeared in the CSF in 13 out of 14 cases investigated. Nevertheless, this finding alone has little diagnostic value as it may be detected in the absence of meningeal invasion.[29,30] Preliminary studies suggest that the quantification of paraprotein in the CSF or the CSF/serum paraprotein index, among other parameters, may be useful as an expression of its intrathecal production.[30]

The treatment is similar to that of other meningeal tumours, cranial or spinal radiotherapy and intrathecal or systemic chemotherapy administered in different combinations. In some patients, including our two cases, control of the meningeal disease was achieved with aggressive treatment of the central nervous system.[13,18,19,21] In the majority, however, the extraneurological disease progressed in spite of systemic chemotherapy, the most frequent cause of death being sepsis associated with severe pancytopenia. All expired within the first three months except for two patients, one of whom died after 10 months[21] and the other who remains alive and disease-free 20 months later.[19] The treatment in these two cases was no different from that of the others. There were no significant differences in the therapeutic response among the diverse plasma cell dyscrasias.

The non-myelomatous plasma cell dyscrasias with meningeal involvement represent a higher percentage than that expected, 33% versus 12%, especially plasma cell leukaemia, which represented 1–2%. Such dyscrasias in general provided 5 of the 27 cases (three from the very start and two after an initial phase of multiple myeloma). The most frequent paraproteins in these individuals are IgA and IgD, whereas IgG was secreted in only one case.

The IgD paraprotein also appears in a greater percentage of cases than expected, 5 out of 27[10,14,26] cases versus 1–2%.[31] Two had plasma cell leukaemia, one disseminated extra medullary plasmacytoma and two myeloma. The extraneurological involvement in these patients was marked, with pleural and testicular invasion being noteworthy in three cases and pulmonary and pericardial invasion in two. Although the IgD paraprotein is associated with a greater extramedullary proliferation, these localizations are unusual in cases without meningeal involvement.[31]

Our cases are, to date, the only cases of IgD-secreting non-myelomatous leptomeningitis diagnosed in life. In one case the diagnosis was made by necropsy.[26]

The analysis of these 27 cases of plasma cell dyscrasias permits us to suggest as factors predisposing to diffuse meningeal invasion: the male sex, the presence of the IgD paraprotein, presentation in the form of leukaemia, and neoplastic involvement of pleura, lung, pericardium and testicle. Plasma cell leptomeningitis is associated with a high death rate. Although it is possible to control the neurological disease in some patients, the majority expire as a result of disseminated disease. The prophylaxis of the central nervous system does not appear to be advisable until an effective treatment, capable of maintaining the systemic disease in remission, or curing it, becomes available.

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Notes