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Monoclonal gammopathies

Clinical outcome of extramedullary plasmacytoma

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ABSTRACT

***Background and Objectives*. The aim of this study was a retrospective analysis of the presenting features of extramedullary plasmacytoma, its response to therapy and its clinical course.**

***Design and Methods.* Forty-six cases diagnosed between August 1970 and June 1993 were carefully reviewed. The follow-up was continued until June 1998 and the median observation time was 118 months.**

***Results.* The disease was most frequently localized in the upper airways (37/46; 80%), with the mass limited to a single site in all but seven patients in whom two contiguous sites were involved. Other localizations were the lymph nodes, thyroid, skin, stomach, and brain. The clinical symptoms were related to the site of presentation, and the median time between appearance and diagnosis was 7.5 months. The median age at diagnosis was 55 years (range 16-80), with 14 patients (30%) being under 50 years old. The disorder was approximately twice as common in males as in females. Ten patients (21%) had a monoclonal component. The therapeutic strategy varied, although the most frequent form of treatment was local radiotherapy. Thirty-nine patients (85%) achieved complete remission (CR), five (11%) a partial remission (PR) and two (4%) did not respond to therapy (NR). Local recurrence (LR) or recurrence at other sites (ROS) occurred in 7.5% and 10%, respectively. Seven patients (15%) developed multiple myeloma (MM), characterized by multiple sites of osteolysis in almost all cases with soft tissue involvement in some of them. The 15 year survival rate was 78%.**

***Interpretation and Conclusions*. This review of a relatively large series of patients confirms the favorable prognosis of EMP when treated locally by irradiation and/or surgery.**

Key words: extramedullary plasmacytoma, localized plasmacytoma, multiple myeloma, monoclonal component

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Extramedullary plasmacytoma (EMP) is a plasma cell tumor which involves soft tissues, without any signs of systemic spread. It may originate in many sites, although most frequently it occurs in the upper respiratory tract and oral cavity.

EMP is present in less than 5% of all plasma cell neoplasms, a percentage similar to that reported for solitary plasmacytoma of bone (SPB).[4,5] Both these tumors are composed of sheets of plasma cells at different stages of maturity, and both respond favorably to appropriate therapy.[6] However, SPB evolves into multiple myeloma (MM) more frequently than EMP.[2,4,5]

Few clinical studies on large series of patients have been reported so far, because of the rarity of EMP.[2] This report analyzes in detail the natural history of the disease in 46 patients with true EMP.

Design and Methods

The records of 46 patients with a diagnosis of EMP established in four Italian institutions between August 1970 and June 1993 were reviewed. All patients who suffer from EMP at the four clinics were included. Histopathologic diagnosis was made from hematoxylin-eosin and Giemsa-stained slides and confirmed by immunohistochemical demonstration of monoclonal cytoplasmic immunoglobulins. Initial work-up included bone marrow biopsy and aspirate, skeletal X-ray survey, serum electrophoresis, immunoglobulin quantification, immunoelectrophoresis or immunofixation of serum and urine, β_2 microglobulin assay (the last two tests were performed when they came into laboratory use), chest X-ray, abdominal ultrasonography, and CT-scan (when available).

The diagnostic criteria were as follows:

1. biopsy of tissue showing plasma cell histology;
2. bone marrow plasma cell infiltration not exceeding 5% of all nucleated cells;
3. absence of osteolytic bone lesions or other tissue involvement;
4. absence of hypercalcemia or kidney failure;
5. low serum M-protein concentration, if present.

The response to treatment was defined as complete, partial or none. The criteria for complete remission (CR) included the disappearance of the tumor mass and the clinical symptoms, as well as the M component, if initially present. Partial remission (PR) was defined as a reduction of the signs and symptoms

related to the disease. No response (NR) meant that the clinical features remained unmodified.

The latest follow-up for all patients was in June 1998. At that time, the median follow-up had been 118 months (range, 14 to 280).

Survival and diffusion-free survival curves were plotted from the diagnosis and the end of therapy to June 1998 using the Kaplan-Meier's method.[7] Differences in survival duration were compared by the log-rank method, using two-tailed *p* values.[8]

Results

Clinical and laboratory features

The distribution of the primary tumor lesions is shown in Table 1. The sites most frequently involved were the upper respiratory tract and the oral cavity, which accounted for 80% of the cases. All patients had only one single site of localization, in 7 of them two sites were contiguously involved. The mean time between the appearance of symptoms and diagnosis was 7.5 months (range 1-36). The symptoms, which were related to the site of the tumor, included: swelling, dyspnea, dysphonia, dysphagia, epistaxis, headache and epigastric pain. The patient's average age was 55 (range 16-80) years old [but 14 (30%) of them were under 50]. The ratio of males to females was 30:17. Serum electrophoresis tests were carried out for all patients and showed a monoclonal component in 10 subjects (21%). Serum immunoelectrophoresis or immunofixation was performed in 38/46 of cases (83%) and in all patients who showed a monoclonal component. The monoclonal component was of IgG type in 9 cases and of IgM type in 1 case. Light chains were of κ-type in 8 cases and λ-type in the other 2. All patients showed normal concentrations of non-involved immunoglobulins. An electrophoresis or immunofixation of a concentrated sample of urine was done in 36 cases, and in all samples the presence of Bence Jones proteinuria was ruled out. β_2 microglobulin concentration was determined in 18 individuals (39%) and was found to be less than 3.0 mg/dL in all cases. The histologic features of the patient with an IgM protein were not different from those with IgG.

Treatment and response to therapy

The therapy varied according to each institution's policy. Twenty-eight patients were treated with surgery, alone (n=6) or combined with radiotherapy (n=14) or chemotherapy (n=3) or both (n=5). The remaining 18 patients received radiotherapy alone (n=14) or radiotherapy plus chemotherapy (n=4). The average dose of radiotherapy was 46 Gy (range 30-60). Chemotherapy was administered to seven patients who presented with a monoclonal component, one with gastric involvement, to one patient who had not responded to another treatment, and to three for arbitrary reasons. In all cases but one, an average of 6 courses of melphalan and steroids was given.

Complete remission was achieved in 39 cases (85%). Partial remission was obtained in five patients (11%): a lower M component persisted in three cases, whereas in the remaining two the tumor decreased in size but did not disappear. Two patients, with disease localized in the brain and ethmoid, surprisingly did not respond to radiotherapy delivered at doses of 46 and 50 Gy, respectively.

Table 1. Sites of localization in 46 patients with EMP.

Upper respiratory tract and oral cavity	
Pharynx	9 (+3 nasal fossae; +1 tongue)
Maxillary sinus	6 (+3 ethmoid)
Larynx	5
Tonsil	5
Nares/nasal fossae	5
Paranasal sinus	2
Velum pendulum palati	1
Ethmoid	1
Gums/oral mucosa	3
Other sites	
Lymph-nodes	4
Skin	2
Thyroid	1
Brain	1
Stomach	1

Table 2. Clinical course of 46 patients with EMP.

		CCR	*CPR*	*LR*	*ROS*	*DD*
CR	39	28	0	3	6	4*
PR	5	2°	2	0	0	1
NR	2	0	0	0	0	2

*CCR = continued complete remission; CPR = continued partial remission; LR = local recurrence; ROS = recurrence at other site; DD = disease diffusion. *Two patients showed ROS before developing DD. °CCR was achieved through surgery of the residual mass after primary treatment.*

Clinical course and survival

The follow-up of the patients is shown in Table 2. During the observation period, 28 of the 39 patients who had achieved CR remained in CR for 3 to 18 (median 9) years. Two patients developed MM. Of the remaining nine patients, three had a local relapse and six a relapse at other sites. Two of the 3 patients who experienced a local relapse (tonsil and larynx), previously treated with surgery and low-dose radiotherapy (30 and 36 Gy respectively), were treated again after their relapse with local radiotherapy (48 and 46 Gy), and obtained a second and stable CR. In the third patient who had the tumor in a nasal fossa, the mass was surgically removed and a second CR was obtained. Of the 6 patients who had a relapse in other sites, 4 still had an extramedullary localization, while the other 2 developed a solitary plasmacytoma of bone. All of them were treated with local radiotherapy at a dosage ranging from 46 to 54 Cy, and all of them achieved a second CR. Subsequently, the 2 patients who had a second bone

relapse progressed to MM, and a third case developed a lymphoblastic lymphoma after 43 months.

Two of the 3 partial responders, in whom monoclonal component persisted, were still in PR without further treatment after 60 and 72 months; the third developed a relapse in another site and subsequently MM. In the two patients in whom a mass persisted, the mass was removed surgically, and histologic examination showed amyloid substance in both cases, localized only to the tumor area. These two patients are in CR.

In non-responding patients, the disease spread within 2 years.

At the time of analyzing these data 37 patients (80%) were alive and nine (20%) had died. Thirty-one (84%) of the survivors were in primary or secondary CR (average of 87 months; range 36-214), 2 of them (5.4%) were still in PR 36 and 48 months after the end of therapy, and 4 of them (10.8%) had MM. Nine patients have died; the cause of death was progression of EMP in 3 patients and unrelated causes in the other 6 (2 gastric carcinoma, 1 gastric hemorrhage; 1 stroke; 1 unknown; 1 lymphoblastic lymphoma). After an average of 40 months (range 10-95), 7 patients (15%) developed disseminated disease, consisting in multiple bone lysis but without any evidence of M-component or of monoclonal marrow plasmacytosis in most cases (Table 3). In two of the 7 cases, dissemination involved both the bone and soft tissues other than from where the tumor had originated (kidney, adrenal glands and liver) with rapid tumor growth, and short survival. The disease became typical MM in only one patient. The therapy for these patients included alkylating agents and glucocorticoids. All 5 patients with only bone involvement responded to alkylating agents therapy and their outcome was characterized by indolent disease with a long mean survival time (98 months). In contrast, the two patients with both bone and secondary soft tissue involvement did not respond to the treatment.

After 15 years, the overall survival was 78% (Figure 1) and the diffusion-free survival was 83% (Figure 2).

Discussion

The present analysis confirms the good response to therapy and the good clinical course of EMP, as reported by other studies.[1-3,9] In fact, the clinical outcome was very favorable with absence of dissemination in 85% of the cases and with 78% of the patients alive after 15 years. Like the series in other previously published reports (Table 4), our population of patients had an average age of 55,[4,5,11] but 30% of patients were under 50 years old, indicating that EMP may affect young subjects in about one-third of cases.

In line with the previous reports, EMP usually developed in the upper airway passages and oral cavity.[1,2,10] However, it was also simultaneously found in contiguous sites confirming that the disease tends to spread locally.[11] The uncommon localizations in the thyroid gland and brain observed in this study prove that the disease may affect any site.[1,2,10]

Local recurrence and new solitary localizations at distant sites were seldom observed (8% and 13%, respectively). However, a second and stable CR was frequently obtained by local radiotherapy, confirming the particular sensitivity of plasmacytoma to irradiation.[2,4,12,13] In fact, in line with other studies, our results demonstrate that the elective treatment for EMP is local radiotherapy and that a dose between 40-60 Gy

Table 3. Clinical characteristics of disease diffusion in patients with EMP.

Pts	*M component*	*Bone marrow plasma cells (%)*	*Osteolysis*	*Extraosseous localization*
1	Present*	<5	≥3	Absent
2	Absent	<5	≥3	Absent
3	Present	10	1	Absent
4	Absent	<5	≥3	Present
5	Absent	<5	≥3	Absent
6	Absent	<5	≥3	Present
7	Absent	<5	≥3	Absent

**Small quantity present at diagnosis; no changes during the course of the disease. °Appeared during the diffusion of the disease.*

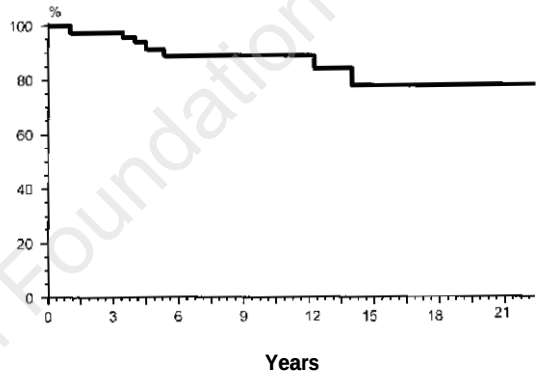

Figure 1. Overall survival of 46 patients with EMP.

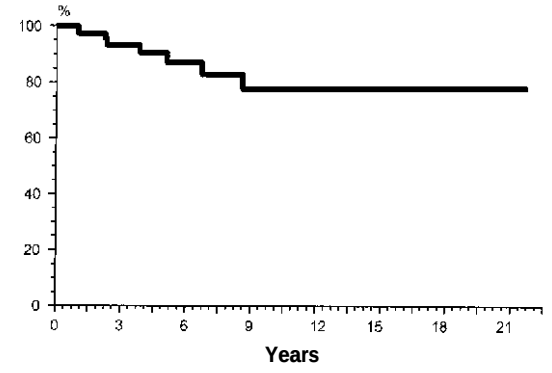

Figure 2. Diffusion-free survival of 46 patients with EMP.

Table 4. Clinical outcome of patients with EMP.

Study	*Corwin and Lindberg 1979*	*Kapadia et al. 1982*	*Knowling et al. 1983*	*Holland et al. 1992*	*Present study*
Number of patients	12	16	25	14	46
Males/females	4/1	4/1	5/1	3.7/1	1.7/1
Median age (yrs.)	–	59	59	58	55
Monoclonal component (%)	16	30	32	–	21
Local recurrence (%)	16	15	–	–	7
Disease diffusion (%)	16	31	16	36	15
Disease-free survival at 10 years (%)	66	–	70	64	78

seems to be sufficient to control the disease,[9,13,14] as indicated by the low frequency of local recurrences observed in this study which in any case occurred only when the level of dose was inferior to 40 Cy.

In this study it is difficult to establish the role of surgery and chemotherapy because of the small number of patients who received this treatment. We did not find any difference in the clinical outcome of patients undergoing surgery and radiotherapy compared with those undergoing radiotherapy alone. However, when surgery was used alone, particularly for a limited and easily resectable mass, no relapses were observed. The development of MM was more frequent in patients who had adjuvant chemotherapy, but most of them had a monoclonal component at diagnosis, indicating a higher risk of disease progression.

Dissemination of EMP occurred in 15% of the patients and this frequently in the first three years, but even as late as 8 years after the completion of therapy. Multiple myeloma originated after EMP was of an unusual type, and only one patient with a primary lymph node localization developed a typical MM. In fact disease dissemination was characterized only by multiple bone localizations that could appear one after another or all together (Table 3). In two cases there was contemporaneous involvement of soft tissues in sites other than those of the tumor origin, indicating that the follow-up of these patients should include periodic bone marrow studies, serum and urine protein evaluation, skeletal radiographic examination, and abdomen ultrasonography or computed tomography (the last examination should be performed during the first three years). This particular pattern of the spread of EMP has already been reported,[2,11] and in our study it represented the typical evolution of the disease. This could be clinical evidence that EMP has a different origin and consequently different biological aspects than MM and perhaps also SPB,[3] despite the fact that all these entities have histologic and immunohistochemical similarities.[1,6]

The presence of paraprotein at diagnosis (p=0.04) but not its persistence (p=0.4) may be an important indicator of dissemination of EMP. It was not possible, however, to analyze this relationship in a rigorous way because of the small number of cases with a M-spike at diagnosis. In contrast to in SPB,[12] β_2 microglobulin concentration was never high and in our population did not appear to be predictive of disease progression; in fact two patients had MM despite low values of β_2 microglobulin. Neither the patient's age nor sex had an influence on the spread of EMP. As expected, disease dissemination was significantly greater in those patients who did not achieve CR (p=0.01). No statistically significant difference in evolution seemed to occur as a consequence of site of localization.[1,10] However, since a lower percentage of patients (4/36; 11%) with upper respiratory tract and oral cavity localizations had disease progression than patients with other sites of involvement (3/9; 33%), a difference may, in fact, exist.

Our findings confirm the good prognosis of EMP. The cure of the disease can be achieved by radiotherapy in almost all cases. Surgical removal of the tumor can be performed, at diagnosis, as sole treatment of small masses and also when local irradiation has not been successful in eliminating the mass, as in the case of a local deposit of amyloid substance or residual disease. Treatment with chemotherapy does not appear to be indicated because it had no effect on the course of EMP, while disease dissemination can be successfully treated with alklyating agents.[2] Single and selected cases of disease diffusion, particularly those with rapid, soft tissue involvement, could benefit from intensive treatment followed by autologous bone marrow transplantation,[15] a treatment recently examined in this journal.[16-18]

Contributions and Ackowledgments

PG and MC designed the study. PG wrote the paper. AP, GA, CB, SN, UC, MB, SR were involved in the recruitment of the patients and contributed to the final version of the manuscript. FL was responsible for the revision of the paper. All the authors gave their critical contribution to the manuscript.

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Potential implications for clinical practice

- The large number of cases and the long follow-up shows clearly the clinical course of extramedullary plasmacytoma and its high percentage of recoveries.
- The paper points out the difference between extramedullary plasmacytoma and multuple myeloma and it confirms the favorable role of a local treatment in this disease.

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