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CASE REPORT

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Outside the box—Surgery for aggressive plasmacytoma in scar

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Abstract

This report introduces the concept of large-scale surgery and reconstruction when all other medical means of treatment have failed. In select cases, this may act as a mode of buying time and allowing the patient to receive second- or third-line treatments.

KEYWORDS

free flap, microsurgery, multiple myeloma, plasmacytoma, scalp reconstruction

1 | BACKGROUND

We describe the course of disease and multidisciplinary treatment of a multiple myeloma patient who presented with a life-threatening plasmacytoma in-scar resistant to conventional treatment. She underwent wide resection with immediate free-flap reconstruction, allowing for early chemoradiotherapy and autologous bone marrow transplant. She survived additional 18 months following surgery.

Multiple myeloma (MM) is primarily a disease of the skeleton and bone marrow (BM). Disease symptomatology is secondary to BM occupation (anemia) and bone destruction (hypercalcemia, renal insufficiency, painful bony lesions). Median survival is 30-60 months with conventional chemotherapy treatment.[1] Extramedullary disease (EMD) may manifest with soft-tissue extramedullary plasmacytomas (EMPs), and these appear in 7%-18% of MM patients at diagnosis and in up to roughly the same percentage during relapse.[2-4] Most of the soft-tissue EMPs result from direct bony tumor extension, and a minority of them result from hematogenous spread, though some might argue these are separate hematological entities. Common locations of EMPs arising from direct extension include the skull, vertebrae, ribs, and sternum.[2-4] The second type of EMD reflects MM cells that have spread hematogenously, effecting most commonly the subcutaneous tissue, followed by liver, breast, kidney, lymph nodes, and the CNS. A third, rarely reported manifestation of EMD is EMPs arising in scar tissue at sites of invasive surgical procedures or sites of bone surgery and fractures.[1-5]

Multiple myeloma patients with EMD have a worse prognosis than those without EMD and commonly fail to respond to conventional chemotherapy, although they may benefit from high-dose therapy.[2,3,6] EMD at presentation poses a higher risk for subsequent EMD at relapse (hazard ratio [HR] = 13), and the presence of extramedullary involvement at any time during the disease course is associated with significantly shorter progression-free survival and overall survival (OS) when treated with conventional chemotherapy (HRs of 3.26 and 1.46, respectively).[2,3] High-dose chemotherapy followed by either autologous or allogeneic hematopoietic stem cell transplantation is investigated as a mode of treatment for this aggressive variant.[1-4,6] Some publications suggest that the inflammatory response evoked by surgery, local trauma, and fracture may create a niche that facilitates

the implantation of MM cells traveling out of the bone marrow.[7-10] Yet after the initial seeding, these tumors proliferate even more rapidly possibly by promoting a microenvironment of low oxygen pressure, neoangiogenesis, and cytokines that favors the more virulent clone.[7]

We would like to present here a case of an extremely aggressive MM aggravated by surgery, refractory to all medical treatment, that following a complex multi-specialty surgery, involving craniotomy and microsurgery achieved prolonged survival.

2 | CASE PRESENTATION

A 63-year-old woman was transferred to our department with a large fungating tumor of the left temporo-parietal scalp diagnosed as MM presenting as an EMP.

Three months earlier, she underwent an excisional biopsy of a slow-growing, subcutaneous nodule on the left frontoparietal aspect of her scalp. The lesion was 1 cm in diameter, purplish in color, firm to the touch, and mobile. The pathologic findings led to the initial diagnosis of plasmacytoma, after which the patient underwent a full hematological workup. The disease was oligosecretory, with no para-proteinemia and a monoclonal population of plasma cells occupying about 30% of the bone marrow cells. PET-CT demonstrated two additional bony lesions in the left 4th rib with an expanding soft-tissue mass and in the 11th thoracic vertebra. Her final diagnosis was summarized as MM with an extramedullary plasmacytoma.

Within several weeks following the initial biopsy, the scalp lesion grew rapidly in the scar, reaching a size of 10 cm in diameter. It spread to the adjacent calvaria creating a full-thickness defect 3 cm in diameter. The lesion was painful, highly vascular with multiple necrotic foci and oozed blood uncontrollably (Figure 1). Palliative radiotherapy (16 Gy in four fractions) was initiated in attempt to control the bleeding but failed to do so. The patient's hemoglobin levels dropped steadily to 6.5 mg/dL, necessitating multiple blood transfusions. Another therapeutic attempt was made, and the patient received two cycles of chemotherapy with bortezomib, cyclophosphamide, and dexamethasone (VCD) with no observable response.

At this point, the patient was transferred to a tertiary facility, where a multidisciplinary team was formed and included hemato-oncologists, radiation oncologists, neurosurgeons, and plastic surgeons. It was felt that the medical treatment for the imminent terminal scalp lesion was exhausted, and therefore, a surgical approach was decided upon. A collaborative approach consisting of neurosurgery performing a wide resection of the tumor and plastic surgery immediately reconstructing the skull and scalp defect.

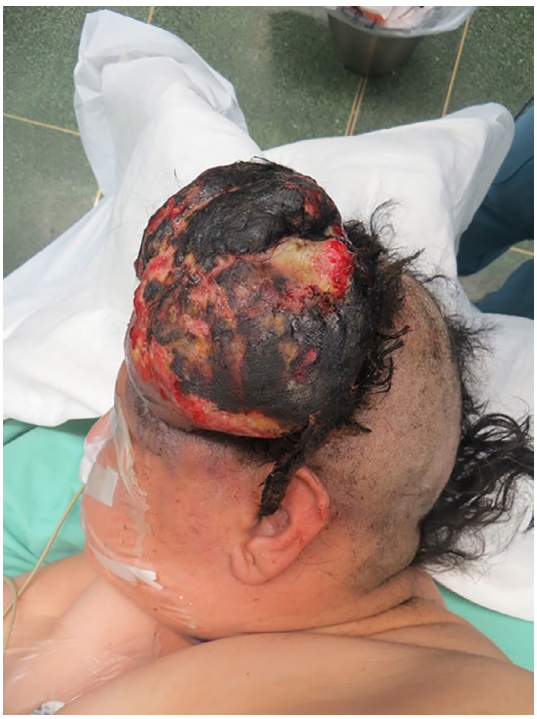

FIGURE 1 Preoperative photograph. Note large exophytic lesion with multiple necrotic foci arising from left parietal scalp

The preoperative evaluation included a head CT that demonstrated a 4.1 × 11 × 10 cm space-occupying lesion in the soft tissue of the scalp with a bone defect of 2.7 × 1.2 × 2.4 cm. The lesion contained multiple hemorrhagic foci, and an MRI study showed homogeneous enhancement of the dura underneath it, suggesting its involvement (Figure 2). A biopsy was obtained from the lesion and showed large cells with plasmoblastic differentiation.

The patient underwent surgery within a week of her transfer (Figure 3). The tumor was resected with 2-cm skin margins, and a wide craniectomy was performed leaving a bony defect of about 5 cm in diameter. The dura did not appear to be involved macroscopically and was therefore left intact. Intraoperative frozen sections were sent for pathologic analysis. The skin showed anaplastic plasmacytoma with resection margins free of tumor. The tumor itself consisted of sheets of pleomorphic cells with an increased mitotic rate. The tumor cells were positive for CD56, CD79a, CD138, and lambda light chains, and negative for CD20, IgM, and kappa light chains. Eighty percent of the cells were positive for Ki-67.[11,12]

The bony defect was covered with a titanium mesh, and soft tissue was reconstructed using a latissimus dorsi muscle free flap covered by a split-thickness skin graft. Anastomoses were performed in an end-to-end fashion between the thoracodorsal vessels and the left superficial temporal vessels. Ischemia time was 90 minutes.

The postoperative period was totally uneventful, the skin graft had taken completely, and the patient recovered rapidly with no medical, neurological, or surgical sequelae

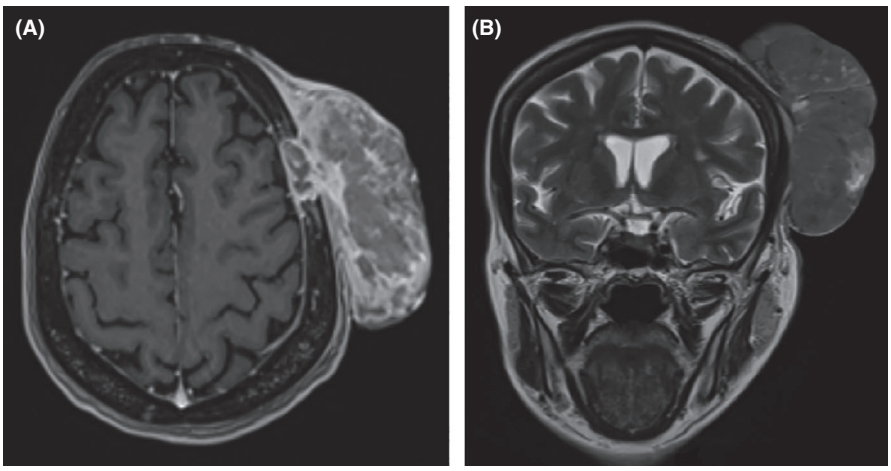

FIGURE 2 Preoperative imaging on MRI. A, showing T1 phase on cross section and B, showing T2 phase on coronal section. Note large exophytic lesion involving scalp skin, subcutaneous tissue, bone with enhancement of the dura on T1

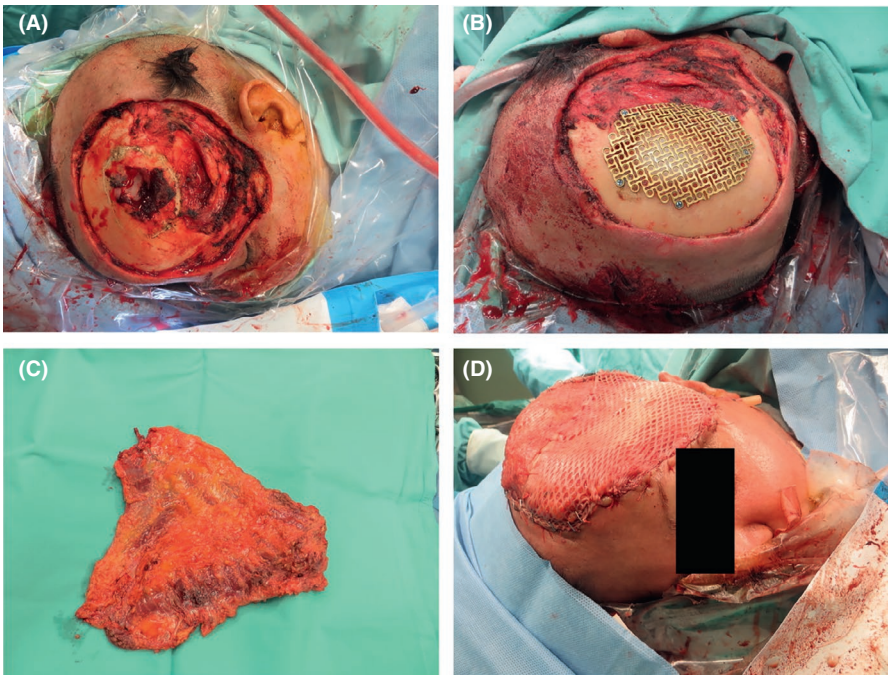

FIGURE 3 Intraoperative photographs. A, Following wide resection of the lesion up to the skull and including craniectomy in the center leaving the dura intact. B, Reconstruction of the bony defect with a titanium mesh. C, Free latissimus dorsi flap following harvest. D, Following insetting of the flap and split-thickness skin grafting

(Figure 4). She was discharged on postoperative day 15 with a stable hemoglobin level of 9.9 mg/dL. Three weeks postoperatively, she began biologic therapy with dexamethasone and Velcade (bortezomib), which she tolerated well. She also received electron beam radiotherapy of 15 Gy in five fractions which was started 5 weeks after surgery, and it had no adverse influence on the surgical outcome.

At this point, the patient underwent a second PET-CT which demonstrated a new 1.4 cm FDG avid cervical lymph node. A biopsy revealed immature monoclonal plasma cells, and the patient was subsequently treated with high-dose melphalan and autologous HSCT with resolution of the cervical lymphadenopathy. Treatment with lenalidomide, carfilzomib, and dexamethasone was later initiated. The patient continued hematology follow-up and treatment however approximately 18 months following surgery succumbed to the disease.

3 | DISCUSSION

It is well known that the BM microenvironment plays a key role in the pathogenesis of MM. Soluble factors mediate myeloma cell proliferation, migration, and survival and induce adhesion of myeloma cells to cellular components of the BM. Intrinsic factors of the tumor cells themselves influence their biologic behavior, aggressiveness, and tendency to metastasize to extramedullary sites. In contrast to BM myeloma cells, or disease arising from direct extensions of a focal bone lesion, plasma cells from metastatic EMPs usually have a plasmoblastic morphology and are less differentiated. Extramedullary MM is most commonly localized to the reticuloendothelial system, while metastatic cutaneous lesions are less common.[3] EMD has become more frequent at diagnosis and at relapse of MM in recent years. This was

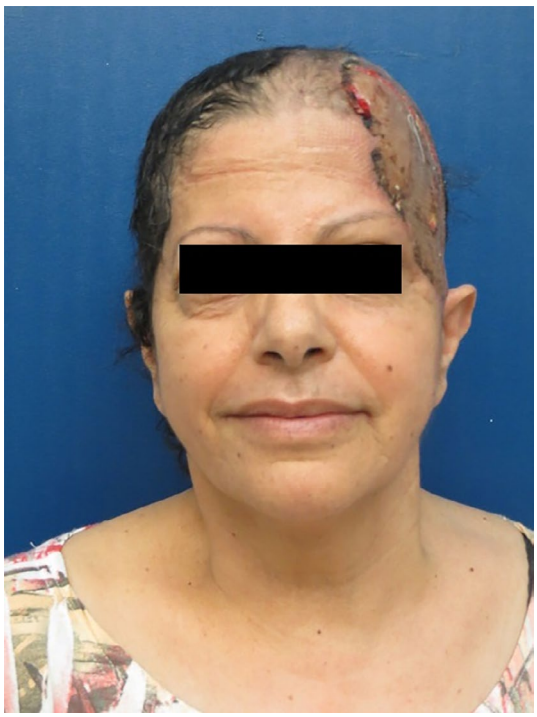

FIGURE 4 Postoperative photograph at 3 mo. Skin graft fully taken on latissimus dorsi free flap, note flap atrophy providing good contour of the neo-scalp

explained by the widespread use of better and more sensitive imaging techniques.[2] It has also been suggested that it is related to the use of high-dose therapy and novel agents that are less effective for EMD and therefore the relapse is expected there.[2,3] The idea had also been raised that treatment with novel agents and HSCT permits a predominance of myeloma subclones that are independent of the BM microenvironment and can therefore thrive in other tissues. These subclones are said to later gain a survival advantage in an active microenvironment, such as the one that appears in the inflammatory milieu of active scars or the foci of trauma.[7] Recent studies, however, do not report any significant increase in EMP rates among patients treated with novel drugs.[2-4,10] A recent multivariate analysis found that the only significant predictor of extramedullary recurrence is EMD at presentation.[3] This supports the notion that extramedullary spread is related to characteristics inherent to the myeloma clone or to the host, rather than to the treatment.[2,3,10]

In addition to the two common mechanisms for extramedullary spread (hematogenous and direct bony extension), EMPs have been reported to arise in scar tissue of invasive procedures. This has been described in scars of laparotomy, catheter, and pacemaker insertion sites, sites of bone fracture, and even sites of blunt trauma.[1,5,7-9,13] It has been speculated that the inflammatory process associated with tissue injury that is present in invasive procedures.

facilitates migration of myeloma cells into the skin.[9,13] Generally, tumor relapse in scar tissue is a rare yet well-known phenomenon that is thought to occur secondary to local implants during the procedure or via hematogenous spread.[7] This has not, however, been reported as being characteristic of MM, and the biological mechanisms responsible for its occurrence have not been studied in depth.[8]

Some case reports have described EMP arising in proximity to fracture sites in bones, possibly representing direct extension of the diseased bone marrow, while others report disease appearance in surgical or traumatic sites noncontingent to bone marrow.[1,5,7-9] In this case, there was clinical evidence of boney involvement underneath the soft-tissue tumor, which seemed to progress inversely—emanating from the adjacent subcutaneous violent clone of cells and penetrating the bone.

As suggested by research, chemotherapy and radiation as well as more novel approaches, involving auto/allogenic bone marrow transplantation, do not achieve long-term eradication of EMPs, especially recurrent ones, let alone those appearing in surgical sites. Yet those will still be the first line of treatment used, in such cases. A recently published consensus of the Chinese Myeloma Working Group[14] regarding surgical management of myeloma bone disease (MBD), recommended the surgical removal of huge and rapidly growing EMPs while aiming to preserve all vital structures in proximity and within the tumor. Very rarely is surgery recommended as treatment for EMP, as reported in solitary parotid lesions, exophytic vocal cord, and eye lid.[15-17] In our case, none of the standard treatments were effectively able to control the growth of this tumor, as it posed an immediate threat to the patient's life from bleeding and infection. Taking the patient to surgery represents a paradigm shift, “buying” time and controlling the urgent hazard, even at the expense of a large-scale surgery, that may not usually be undertaken in view of an aggressive systemic disease. The surgery reported here in itself is no novelty for scalp reconstruction, yet the agility of all caretakers—haemato-oncologists, plastic surgeons, and neurosurgeons suggesting and undertaking this procedure, though not a common practice, enabled the rapid administration of the wider treatment of chemotherapy and HSCT and gaining additional 18 months of life.

4 | CONCLUSIONS

Soft-tissue EMP is a presentation of MM that usually indicates a more aggressive biological behavior of the tumor, resulting in poorer prognosis and shorter disease-free survival. In cases of solitary masses that are uncontrollable with conventional means and may curtail survival ad hoc, we urge to consider rapid surgical intervention. This, in turn, may allow later initiation of chemoradiotherapy, HSCT, and maintenance chemotherapy for achieving prolonged survival. In the case presented above, we must mention the patient's compliance

and willingness to undergo such complex surgery in order to later continue and receive systemic treatment. Both hematologists and surgeons should bear this option in mind despite the grim prognosis and the deteriorated general condition of such patients. Saying so, surgery itself is not without its risks for complication, failure, and even death; therefore, patient selection should be employed to those who can withstand such a demanding procedure.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

EF: contributed to this work by reviewing the literature, obtaining patient consent, and writing the manuscript. AZ: contributed to this work by reviewing the manuscript. YCC: contributed to this work by reviewing the manuscript. YS: contributed to this work by reviewing the manuscript. EG: contributed to this work by reviewing the manuscript. RY: contributed to this work by obtaining consent, writing, and reviewing the manuscript. All authors have contributed to the study design, drafting, and reviewing of the manuscript and have approved it and its submission.

ETHICAL APPROVAL

The authors declare conforming to the Declaration of Helsinki. Local Institutional Review Board No. 0049-18-TLV.

DATA AVAILABILITY STATEMENT

The complete data regarding this patients clinical course and treatment including imaging, pathological specimens, laboratory findings, etc are found at Tel Aviv Sourasky Medical Center's computerized database and Pathology Institute. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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