Plasmacytoma and Multiple Myeloma

6

Richard Tsang

Abstract

In this chapter, two challenging cases of plasma cell neoplastic diseases are presented. The first is a solitary plasmacytoma, diagnosed in a setting of POEMS syndrome (Dispenzieri, Am J Hematol 89(2):214–223, 2004). This illustrates the potential curative nature of radiation therapy in this rare disease. The second case is the more common multiple myeloma, treated with systemic chemotherapy and autologous peripheral blood stem transplantation, but with unusual spread to the central nervous system. The case presentations will be followed by a discussion of the salient clinical evaluation and management in each case, with a focus on the role of radiation therapy and the sequencing of various therapies applied in these unusual and challenging clinical scenarios.

Clinical Presentation 1: Solitary Plasmacytoma of the Scapula in a Patient with POEMS Syndrome (*P*olyneuropathy, *O*rganomegaly, *E*ndocrinopathy, *M*onoclonal Plasma Cell Disorder, and *S*kin Abnormalities)

A 60-year-old woman presented with numbness and progressive weakness of her legs over 3–4 months. She also complained of some weight loss and blurriness of vision. When assessed by an ophthalmologist, she was diagnosed with papilledema, cause unidentified. She developed diabetes mellitus requiring an oral hypoglycemic. Her leg weakness progressed to the point where she was not able to walk, and her arms started to be weak too. She was found to have a thrombocytosis between 640 and 860×10^9/L. She had further weight loss of 30 lbs and had developed generalized edema affecting her body (anasarca). At this time, about 12 months after her initial symptoms, she was admitted to hospital for investigations and saw a hematologist who suspected POEMS syndrome and a plasma cell proliferative disorder. She had a significant past medical history of (1) IgA nephropathy with chronic renal failure 14 years previously and treated initially with hemodialysis for 5 years and then a renal allograft transplant. She was

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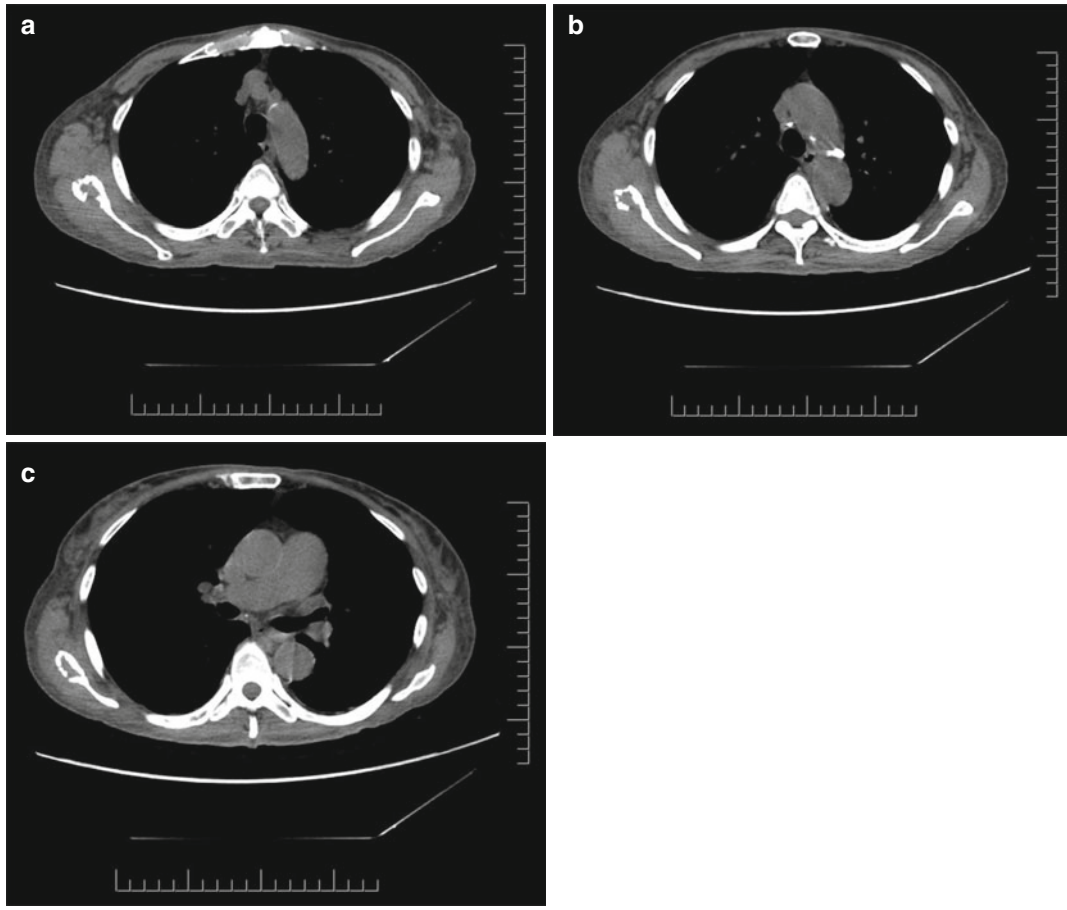

Fig. 6.1 (**a**–**c**) Axial CT scan slices showing a mixed sclerotic lytic lesion in the right scapula. There was associated soft tissue swelling in the surrounding musculature

maintained on immunosuppression with mycophenolate mofetil and tacrolimus. (2) Transient ischemic attack 1.5 years previously with complete occlusion of the right internal carotid artery on ultrasound, no sustained neurologic deficits.

Her clinical examination confirmed bilateral papilledema, a bilateral symmetrical sensory motor neuropathy of both arms and legs (worse in legs), a borderline enlarged right cervical lymph node (1.5 cm) but no other lymphadenopathy, moderate anasarca, and splenomegaly. She has no skin changes or other organomegaly noted. She denied bone pain. Her ECOG performance status was 4 because she was completely bedridden. Her investigations showed the following: normal hemoglobin and white cell count and platelets elevated as above. Albumin was low at 29 g/L. Serum creatinine, calcium, liver function tests, and $\beta_2$microglobulin were all normal. HIV test is negative. Electromyography testing confirmed a severe demyelinating sensorimotor polyradicular neuropathy. Her skeletal survey and CT and MR scans showed a 4 cm (transverse) × 7 cm (craniocaudal) lytic-sclerotic lesion in the right scapula (Figs. 6.1 and 6.2), with an associated soft tissue mass in the surrounding musculature. There were no skeletal abnormalities elsewhere. CT scan also confirmed splenomegaly and moderate ascites, but no generalized lymphadenopathy apart from the borderline right cervical lymph node. Blood and urine were negative for monoclonal proteins, and serum light chains were normal.

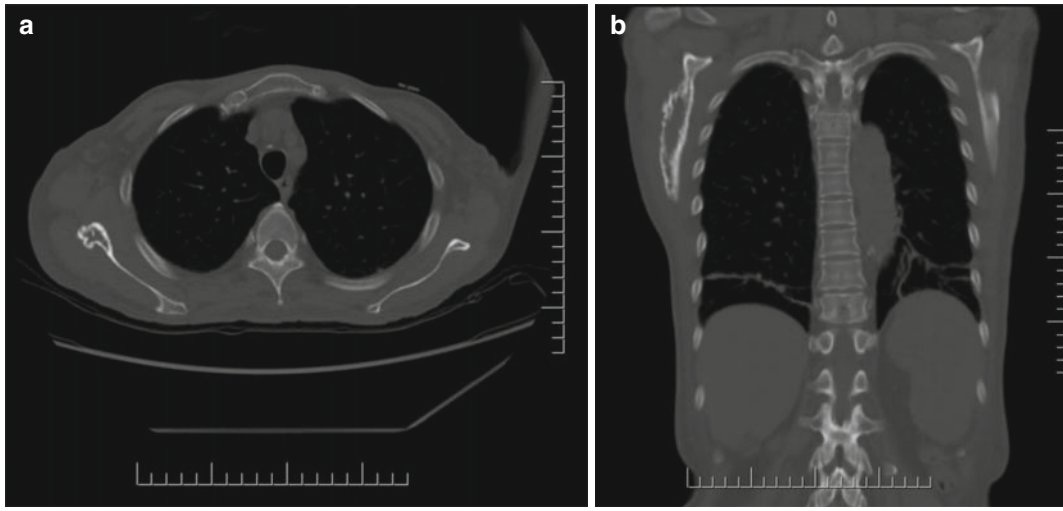

Fig. 6.2 Axial (**a**) and coronal (*right panel*) CT scan with bone windows, showing the partly sclerotic and partly lytic nature of the lesion. Note splenomegaly in the coronal CT (**b**)

Bone marrow biopsy shows mild hypercellularity, but plasma cells were normal (<5 %). There was no evidence of multiple myeloma. A biopsy of the right scapula mass showed plasmacytoma, with the abnormal plasma cells lambda restricted, and a low Ki-67 proliferation rate of 3 %. Biopsy of the right neck node revealed Castleman's disease, multicentric type. FDG-PET scan showed solitary uptake in the right scapula lesion, with SUV_{max} value 24.3 (Fig. 6.3). Subsequently she also had an elevation of serum vascular endothelial growth factor (VEGF) documented. She was diagnosed with POEMS syndrome, with a solitary plasmacytoma involving her right scapula. There was no evidence of multiple myeloma.

The Diagnosis of POEMS Syndrome and Solitary Plasmacytoma

POEMS syndrome is a rare condition with the acronym representing some (but not all) key paraneoplastic features of the syndrome: *p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *m*onoclonal plasma cell disorder, and *s*kin abnormalities. There are established diagnostic criteria with the mandatory ones being polyneuropathy and a monoclonal plasma cell disorder [1]. In addition, one of three major criteria and one of six minor criteria are required to secure the diagnosis [1]. In this case, the solitary plasmacytoma serves as one of the mandatory criteria, despite the absence of systemic multiple myeloma [1]. The co-diagnosis of Castleman's disease and a sclerotic bone lesion serves as major criteria. Bone lesion, if present in POEMS syndrome, is characteristically sclerotic [2], in contrast with solitary plasmacytoma without POEMS that is typically a purely lytic lesion. She also has a plethora of minor criteria conditions, characterized by splenomegaly (organomegaly), diabetes (endocrinopathy), thrombocytosis with prior thrombotic disease, papilledema, and edema. However she did not have characteristic features of skin changes such as hyperpigmentation or acrocyanosis [3] nor pulmonary manifestations [4]. Patients with POEMS syndrome have these disparate symptoms and signs, and it is quite common to have some typical features but not others, which is the reason why it is difficult to diagnose, in addition to its rarity (prevalence <0.5 per 100,000). Delays in establishing a diagnosis is unfortunately common with median time from onset of symptoms to diagnosis of 19 months in a series of 38 patients [5], similar to that observed in this case. The pathogenesis of POEMS is poorly understood, but it is known

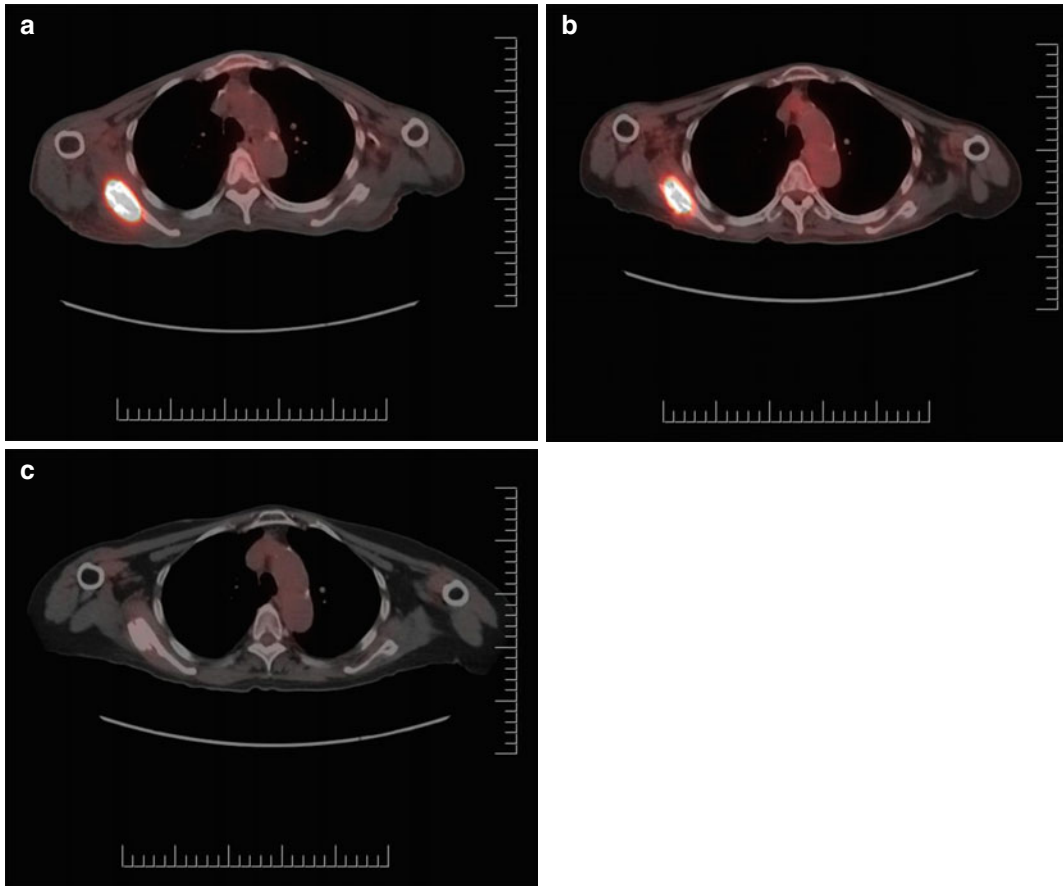

Fig. 6.3 PET/CT scan (axial slices) at initial diagnosis (**a**, *left*), 6 months (**b**, *middle*) and 16 months (**c**, *right*) after radiation treatment (35 Gy). The right scapula osteosclerotic solitary plasmacytoma is avid for FDG uptake with SUV_{max} of 24.3 prior to RT, decreasing to 10.7 at 6 months, and became normal (1.4) at 16 months, and metabolic local control was maintained at 4.5 years follow-up. However some sclerosis of the bone persisted

that treating the underlying monoclonal plasma cell disorder can result in improvement of the syndrome [1, 6, 7]. There is no documentation of IgA nephropathy to be associated with development of POEMS or plasma cell diseases, although one can speculate whether the immunosuppression might have a role in her developing the plasma cell neoplasia. It appears that elevated VEGF levels reflect the disease activity, but anti-VEGF therapy alone has not been successful suggesting that it is another manifestation of the disease rather than having a causative role [1].

The workup of a suspected diagnosis of solitary plasmacytoma is directed to exclude multiple myeloma. The following criteria must be satisfied: a biopsy-confirmed single lesion with negative skeletal imaging elsewhere, normal bone marrow biopsy (<10 % clonal plasma cells), and no myeloma-related organ dysfunction (normal blood counts, calcium and renal function) [8, 9]. A monoclonal protein can be present in blood or urine, but it is usually only minimally elevated. Solitary plasmacytomas present more commonly in the bone, and usual symptoms are pain, neurologic compromise (e.g., from vertebral lesion causing nerve or spinal cord compression), and sometimes pathologic fracture. It is unusual to be locally asymptomatic as in this case with the scapula lesion. Solitary plasmacytoma uncommonly presents in an extramedullary site (20 %), usually as a soft tissue mass in the head and neck

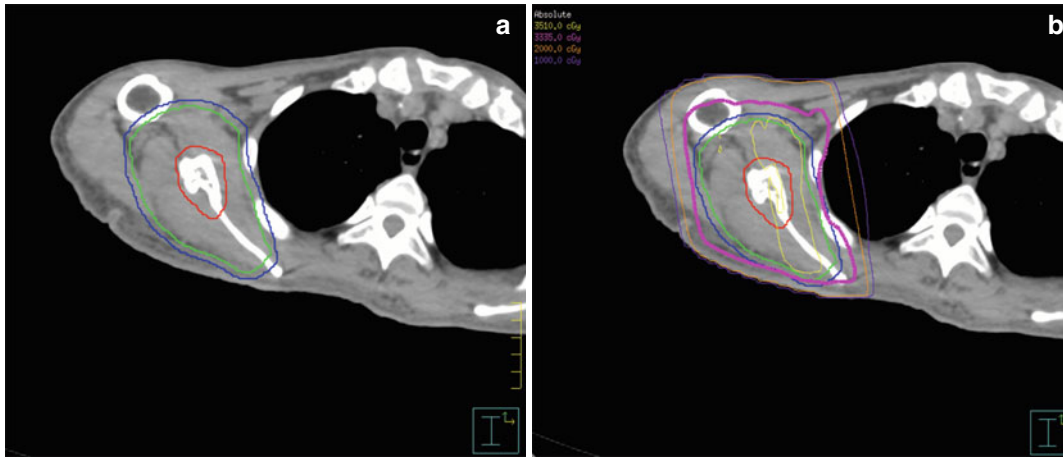

Fig. 6.4 Radiation treatment of right scapula plasmacytoma. (**a**) *Left panel*: Contours of the bony GTV (*red line*), CTV (*green line*), and PTV (*blue line*). (**b**) *Right panel*: Isodose distribution, with prescribed dose 35 Gy and the objective of PTV covered by the 95% isodose line 33.25 Gy

areas [10]. After adequate local treatment, it is known that an extramedullary presentation is associated with a lesser probability of progression to multiple myeloma [10], in contrast with a bone presentation where the disease recurs as multiple myeloma with a high likelihood, usually within 5–10 years [9, 11].

Treatment Management

When the patient was assessed for radiation therapy, she was severely disabled and totally bedridden (ECOG performance status 4) due to her neuropathy and generalized edema. She required frequent care in hospital, and have not experienced any improvement following multiple pulse treatments with high-dose glucocorticoids and intravenous immunoglobulin treatment. It was elected to treat her with radiation therapy to the right scapula lesion, her only documented plasmacytoma. She received 35 Gy in 15 fractions (2.33 Gy fractions) over 3 weeks. This shorter regimen was chosen as she required inter-hospital transfer daily for her RT. Other acceptable regimens in common use are 40–45 Gy in conventional fractionation. However one of the largest multi-institutional reviews showed no evidence of dose response beyond 30 Gy in terms of local control, regardless of size of the tumor [11]. A 3D conformal treatment plan was used choosing beam angles and segmental fields to minimize lung exposure (Figs. 6.4 and 6.5). She tolerated RT well and was transferred to a rehabilitation facility following completion of radiation. At 6 months follow-up, she improved neurologically with recovery in her arms, but still unable to walk. Her edema resolved. Her serum VEGF level returned to normal. Repeat FDG PET/CT scan showed improvement in the scapula lesion, SUVmax decreased to 10.7 and no new lesions detected. Repeat bone marrow biopsy remained negative. One year following RT, she started to ambulate and was able to be discharged home. Repeat FDG PET/CT scans 16 months and 21 months post-RT showed complete metabolic response (no visual uptake in the right scapula), although CT scan continues to show some residual sclerosis at the local site. The patient functioned well apart from residual mild leg weakness.

Four years after RT, she experienced some worsening of her motor strength, and investigations revealed a recurrence of her POEMS syndrome with multiple FDG PET-avid spinal sclerotic lesions (Fig. 6.6) which were new, although small and asymptomatic. The scapula lesion remained controlled with no FDG uptake. She had elevation of serum VEGF (875 pg/ml).

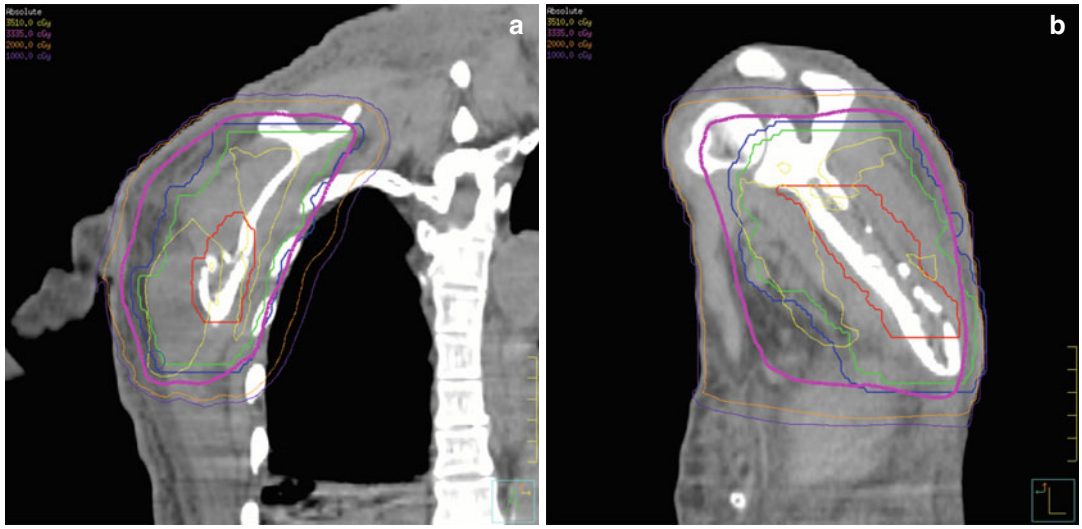

Fig. 6.5 RT treatment of right scapula plasmacytoma. Isodose distributions on CT coronal perspective (**a**) and sagittal perspective (**b**) and bone windows. The sclerotic lytic nature of the lesion is best appreciated on the sagittal image

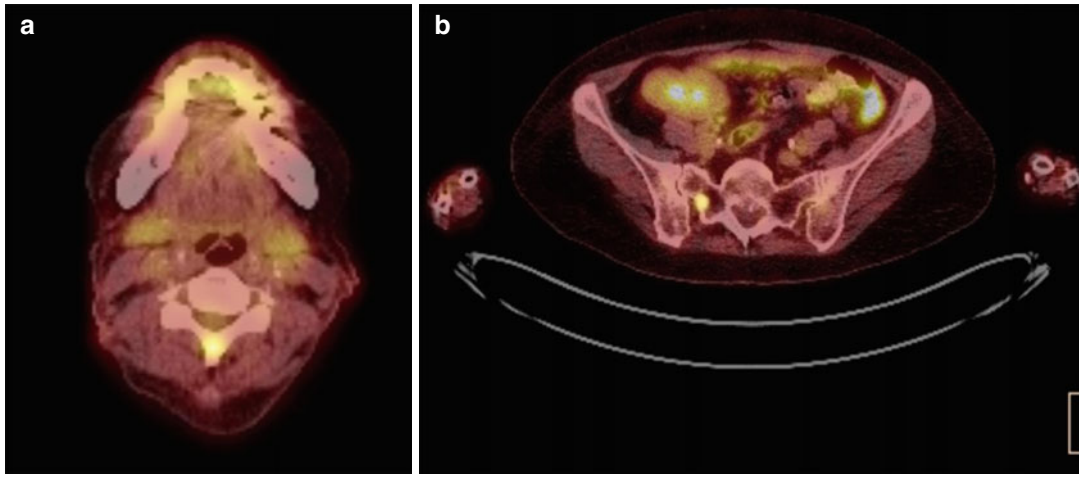

Fig. 6.6 PET/CT scan (axial slices) at time of relapse of disease, 4 years after radiation therapy to the plasmacytoma of the right scapula, showing multiple bone lesions in the spine, with FDG uptake at C5 spinous process (**a**) and right sacroiliac joint (**b**)

However her bone marrow biopsy remained negative for multiple myeloma, and she maintained absence of M-protein in blood and urine. After a brief course of chemotherapy with oral cyclophosphamide and prednisone, she received an autologous peripheral blood stem cell transplant with conditioning regimen consisting of melphalan 200 mg/M^2 and tolerated it well. Her further follow-up is awaited.

Discussion

Radiation therapy is the standard treatment for solitary plasmacytoma. In the presence of POEMS syndrome, provided that there is no evidence of a bone marrow plasma cell clone, radiation therapy is the best initial treatment, even for up to three isolated bone lesions. In one of the largest series of POEMS patients from the Mayo

Clinic ($n=146$), 38 patients (26%) satisfied this criteria and hence was found suitable for radiation therapy (RT) [5]. After median RT doses of 35–54 Gy (median 45 Gy), up to half of patients had clinical improvement or stability of POEMS-related symptoms, but most have some residual disability as in this case. With median follow-up of 43 months, the 4-year overall survival was 97%, although eventually 48% of patient required subsequent salvage therapy due to neurologic deterioration or worsened bone disease [5]. Most were treated with autologous stem cell transplantation, as in this case [12]. The expected 5-year progression-free survival is 75% with transplant [12]. The pretreatment disease features associated with a poor prognosis were pulmonary impairment with a DCLO <75% and elevated urinary total protein [5]. The case described in this report did not have these adverse features. Response to RT is also prognostic, not surprisingly, but as the case illustrates, residual sclerosis persist for many months to years after treatment, not indicative of disease, and this makes routine radiographs or CT scans difficult as a means to assess for residual disease. FDG PET is very helpful in this regard, but the response is very gradual as observed in this case, with a slow decrease in metabolic activity over a period of a year, with disappearance of metabolic activity only after 16 months from completion of RT. Local control has been maintained even when the patient progressed with multiple sclerotic lesions in her thoracic spine, as demonstrated by lack of FDG uptake in the scapula prior to her receiving the autologous stem cell transplant.

Although it is common practice to give a higher dose than 30–35 Gy for solitary plasmacytoma, with some historical data showing a lower local relapse rate of 6% with doses of ≥40 Gy, compared with 31% for lower doses [13], a large series from multiple institutions showed no evidence of improved local control with doses ranging 30–50 Gy, even for tumors >4 cm in maximum diameter [11]. In the case under discussion, a dose of 35 Gy in a slightly hypofractionated regimen have resulted in local control with a 4.5 years follow-up duration from RT. In general, a local control rate of 85–90% is expected from RT for solitary plasmacytoma. Gross target volume and clinical target volume require careful definition of the bone disease and soft tissue infiltration, if present, taking care to encompass adjacent bone which may contain microscopic disease; this can be done using an MRI and following the abnormal signal seen in the bone/bone marrow to include it in the CTV; this is based on the fact that myeloma is a marrow disease, and initially it starts by forming a tumor collection before it gets to produce the lytic lesion that can be seen on CT or to much lesser degree on a simple X-ray. As a general rule CTV is made by adding information from PET scan (avid sites) + MRI abnormal signal in the marrow + CT scan (typically lytic abnormality). In general PTV would vary depending on the site to be treated taking into consideration internal organ motion as well as daily setup, but generally no more than 2 cm is to be added if bone site is considered. Coverage of the whole bone is not required. In general regional nodes are not required to be covered as nodal failures are rare, with the exception that if the plasmacytoma was extramedullary and involve a lymphatic structure (e.g., Waldeyer's ring), the drainage lymph node region deemed at high risk of subclinical disease may be treated.

In summary this case illustrates the usefulness of definitive radiation therapy for solitary plasmacytoma, complicated by a rare debilitating paraneoplastic POEMS syndrome. Dramatic improvement in the POEMS syndrome was observed following RT, although this can take many months. Relapse of the disease with new bone lesions occurred and salvage treatment with an autologous peripheral blood stem cell transplant was required 4 years after the initial treatment.

Clinical Presentation 2: Relapse of Multiple Myeloma in the Central Nervous System

A 58-year-old man presented with a 2-month history of diffuse bone pain. He was traveling abroad and sought medical attention and was found to be anemic. By the time he returned home, he was

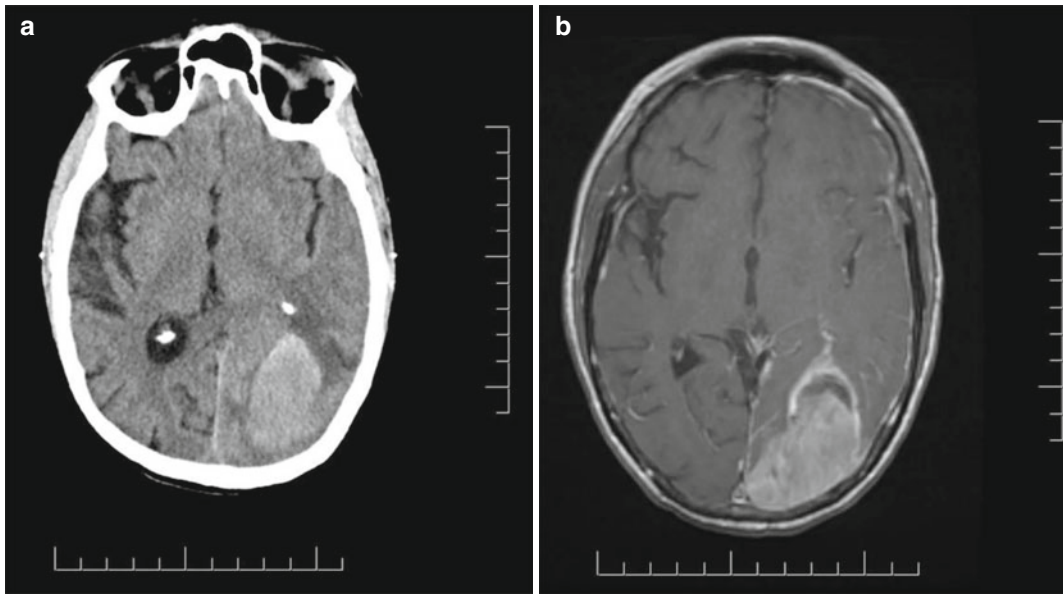

Fig. 6.7 Relapse of myeloma with an extramedullary plasmacytoma of the brain, with a left parietal-occipital mass on CT scan (**a**) and MR scan (**b**, T1 imaging). Mixed area of hemorrhage is evident within the mass. There was minimal midline shift

unwell with anorexia, fatigue, and worsening bone pain. He presented to emergency department and was hospitalized for investigations. He was found to be anemic (hemoglobin 89 g/L) and slightly hypercalcemic (2.66 mmol/L), with a high total protein and low albumin (29 g/L). He was in renal failure with serum creatinine 243 umol/L. Imaging with CT/MRI scans showed multiple lytic lesions throughout his skeleton. Serum protein electrophoresis shows a major M-spike of 73 g/L, an IgG kappa. Bone marrow biopsy showed 80 % infiltration with clonal plasma cells, kappa restricted. There were no adverse cytogenetics findings [such as t(4;14), t(14;16), del17p, etc.] by fluorescent in situ hybridization. His β_2 microglobulin was elevated to 14.3 mg/L. A diagnosis of multiple myeloma was established, and he had stage III disease according to the international staging system [14]. He was initiated on systemic chemotherapy with cyclophosphamide, bortezomib, and dexamethasone (CyBorD regimen) for five cycles, along with pamidronate on a monthly basis. He had improvement in his condition, and his M-protein dropped dramatically to <2 g/L. His bone pain resolved, and he did not require radiation therapy; however he did receive vertebral kyphoplasty to some of his lumbar vertebra. Six months following initial diagnosis, he received an autologous peripheral blood stem cell transplant with the conditioning regimen of melphalan 200 mg/M^2. Posttransplant he remained in complete remission of his myeloma and was started on maintenance lenalidomide 5 mg daily. He developed deep venous thrombosis and was started on anticoagulation treatment. Eight months after stem cell transplant, he started to have visual disturbance and also headaches and vomiting. He presented to the emergency department, and CT and MR scans show a large left occipital mass with hemorrhage (Fig. 6.7). A craniotomy was performed and tumor was resected, and the pathology showed plasmacytoma. Postoperative CT scan showed gross tumor removal was achieved (Fig. 6.8). A lumbar puncture showed that cerebrospinal fluid contained

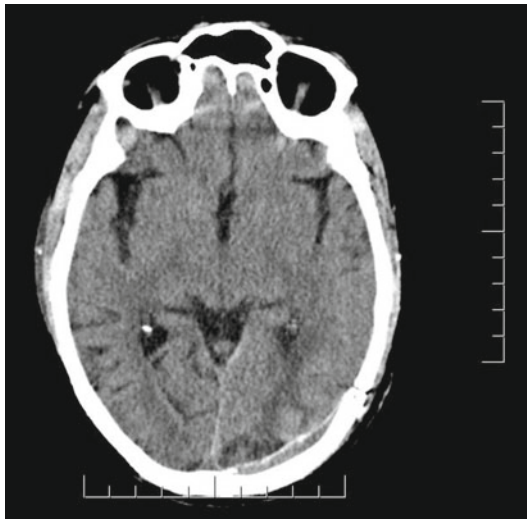

Fig. 6.8 CT scan postsurgical resection of the plasmacytoma of the brain. No residual gross disease was evident. There was minor postsurgical change along the dura in the left occipital area

numerous abnormal monoclonal plasma cells. His serum and urine M-protein remained very low, with no evidence of systemic myeloma on repeat bone marrow biopsy.

Treatment Management for CNS Disease

Central nervous system (CNS) involvement by myeloma is rare, although there are a number of case reports in recent years within the era of novel agents being commonly used in this disease with some prolongation of survival [15–17]. The development of CNS myeloma can be in the form of parenchymal brain disease and/or leptomeningeal involvement. Dura masses, often as a result of a lytic lesion in the skull bone, may be associated with a soft tissue mass which can compress or invade into the dura and should not be considered as true CNS disease. However, such dural involvement if obviously infiltrating through the dura and invading into brain or spread through the leptomeninges should be properly regarded as CNS disease. The CNS could be a relative sanctuary site for the novel agents in myeloma, such as the immunomodulatory drugs (thalidomide, lenalidomide) and the proteasome inhibitors (bortezomib, carfilzomib). In the case illustrated in this review, the patient has relapse of disease confined to the CNS with no detectable recurrence in the bone marrow. Therefore, following multidisciplinary review of treatment options, despite the expected poor prognosis, it was elected to give CNS-directed therapy with intrathecal (IT) chemotherapy to clear the CSF first, followed by consolidative craniospinal radiation. Through an intraventricular Ommaya reservoir inserted by neurosurgery, the patient proceeded with three doses of triple intrathecal chemotherapy with methotrexate 12 mg, cytarabine 40 mg, and hydrocortisone 15 mg, given over 2 weeks. His CSF became clear of plasma cells. Two additional IT treatments were given, and this was followed with craniospinal radiation therapy 30 Gy in 15 fractions to the brain, and the spinal dose was a slightly lower 24 Gy in 15 fractions. Lateral opposing fields were used to treat the brain and cervical spine, with a direct PA field (and segments) to the rest of the whole spine matched for divergence (Fig. 6.9). The junction was moved for a distance of 1 cm twice, after 5 and 10 fractions. Moderate doses were chosen as a trade-off between maintaining effectiveness for CNS control following clearance of the gross disease (in the brain with surgery and the CSF disease by IT chemotherapy) while attempting to limit toxicity for both acute (esophagus, bone marrow reserve), and late effects. The dose-volume histogram with target dose of 30 Gy to the brain is shown in (Fig. 6.10). The patient had completed therapy and further follow-up is awaited.

Discussion

In general the predominate role of radiation therapy in patients with multiple myeloma is for bone pain due to lytic bone disease, if it had not been well controlled on systemic chemotherapy, and for any neurologic compromise due to spinal cord or nerve root compression in the vertebral column or base of skull [8]. Palliative regimens

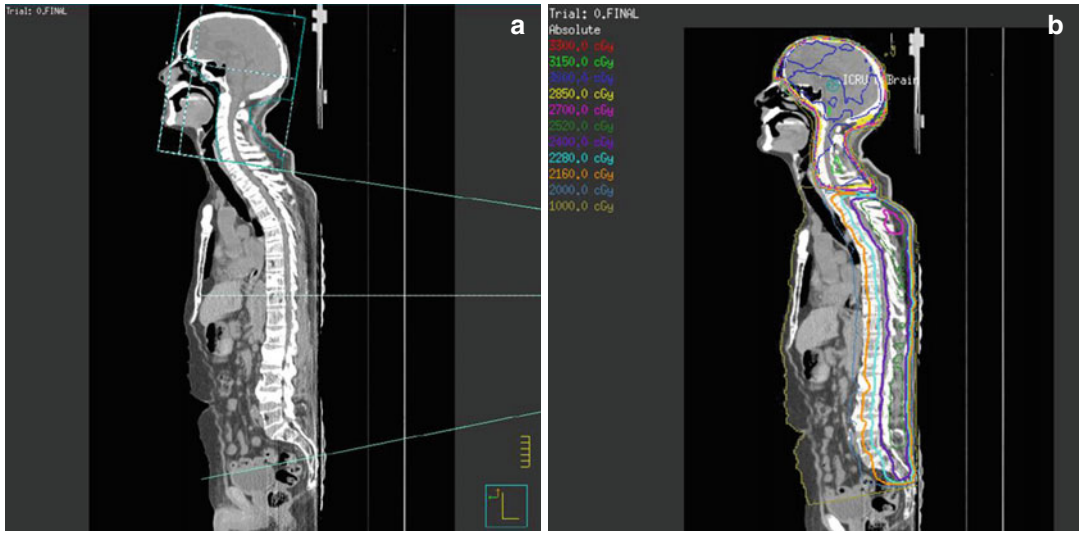

Fig. 6.9 Craniospinal radiation treatment. Lateral opposing fields treat the brain and cervical spine, with collimator rotation to match the divergent PA spinal field (**a**) and the isodose distribution (**b**) with the cranial dose 30 Gy and the spinal dose 24 Gy (given over 3 weeks)

of 10–30 Gy given over 1–3 weeks have been effective, and repeat treatments for the same bony site are seldom required [18]. It should be noted that for palliative bony sites, the target should be limited only to the gross disease noted on imaging with a margin. This is particularly important to avoid unnecessary radiation dose to the marrow causing myelosuppression and possible long-term myelofibrosis in a patient population where future systemic therapy is the mainstay of their treatment.

For spinal cord compression, a longer fractionated course (30 Gy in 10–15 fractions over 2 weeks) may give a better functional outcome than a shorter course [19] . Despite the incurable nature of multiple myeloma, even with 1–2 autologous stem cell transplantation procedures, the use of novel agents and the sequencing of different agents together with use of maintenance therapy have improved the survival rate of contemporarily treated patients [20]. Perhaps this explains the emergence of the more frequent observation of disease progressing to extramedullary sites such as the CNS, as a possible sanctuary site to chemotherapy [15–17]. Treating CNS disease is a challenge as these patients tend to be older (median age of patients with myeloma at diagnosis is over 60 years) and have been heavily pretreated, some with significant medical comorbidities and also complications of their myeloma treatment such as neuropathy or thrombotic disease (as in this case). Also there could be systemic relapse of the disease and also the complications of extensive lytic bone disease to be managed at the same time. In the case under discussion, the patient is relatively young (under 60) and has no systemic relapse of myeloma. There were both parenchymal and leptomeningeal diseases, and the tumor cells adopted a high proliferation rate by histologic assessment. Therefore the clinical decision was made to offer aggressive CNS-directed therapy to optimally control the CNS. From a review of a series of 37 patients with CNS myeloma, it appeared that approaches incorporating CNS radiation produced the best CNS control and also survival duration of >1 year [17]. Several of the "longer-term" survivors were treated with craniospinal radiation to doses of up to 30 Gy [17]. However one must keep in mind that the overall median survival expected is still short, in the range of 2–4 months, and only 9 (out of 37) patients survived for a duration of more than 1 year (median 17.1 months, range 1.1–5.6 years) in one series [17].

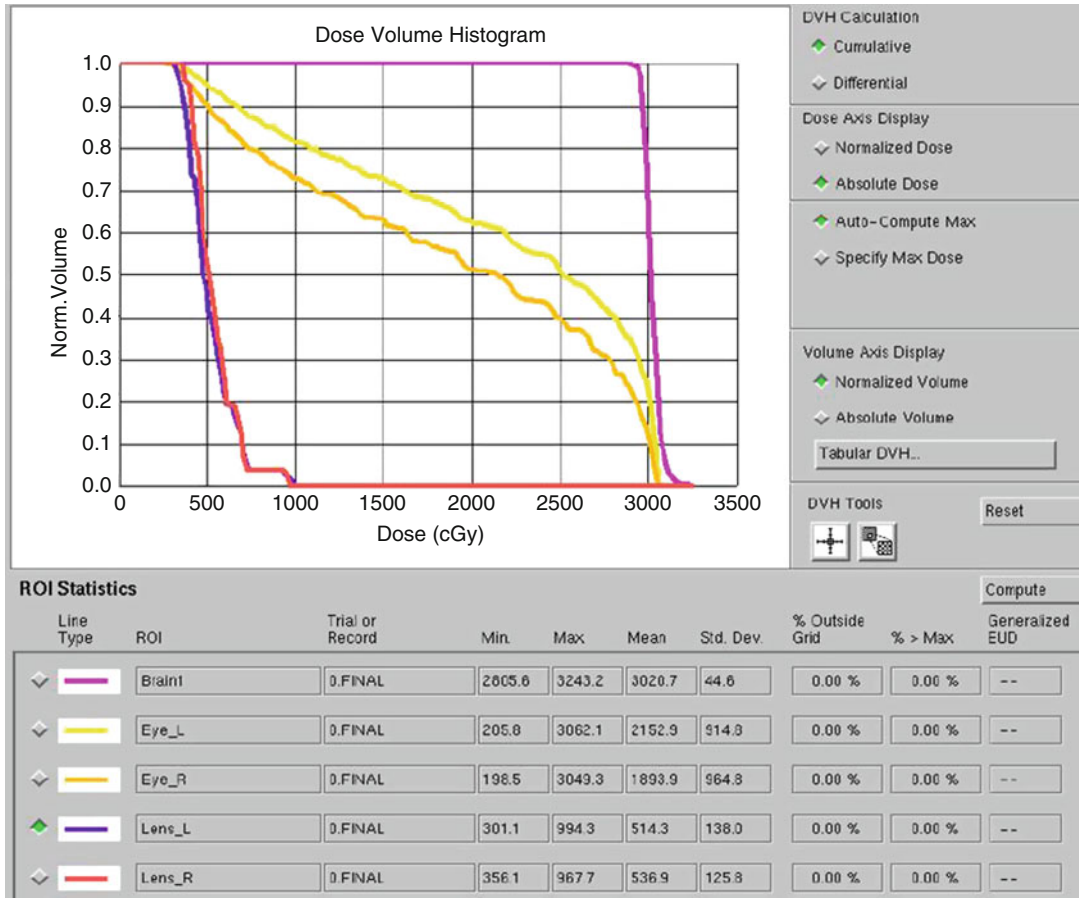

Fig. 6.10 Dose volume histogram showing brain target dose 30 Gy and the eye and lens doses

Conclusions

In summary, the two challenging cases presented in this report illustrated the effective use of radiation therapy in solitary plasmacytoma, under the rare circumstance of a paraneoplastic POEMS syndrome, and also an infrequent observation of multiple myeloma with spread to the central nervous system. While the usual and common use of palliative radiation therapy for bone disease is hardly considered "challenging," with the advent of effective novel systemic treatments for myeloma and patients living longer with their disease, unusual circumstance will continue to arise where radiation therapy may play an important role in management, as well as considerations with sequencing with other therapies and also devising overall treatment plans that are effective and yet safe.

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