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LETTER TO THE EDITOR

CYBERKNIFE® SYSTEM: A NEW THERAPEUTIC STRATEGY FOR SINONASAL SOLITARY EXTRAMEDULLARY PLASMACYTOMA

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Sino-nasal solitary extramedullary plasmacytoma (EMP) is a rare neoplasm with unpredictable progression to multiple myeloma. To improve the precision of irradiation delivery, preserving the healthy surrounding tissue and critical structures we used a CyberKnife® for the treatment of sinonasal solitary extramedullary plasmacytoma. We present the first case of sinonasal-EMP treated with CyberKnife®-stereotactic radiotherapy (SRT) with a complete remission without adverse events. Based on the post-therapeutic results and healthy tissue preservation, we believe that CyberKnife®-SRT represents a good therapeutic option for the treatment of sinonasal-EMP.

To the Editor,

Plasma cell neoplasms, characterized by a proliferation of a single clone plasma cells producing monoclonal immunoglobulins, are cytologically and immunophenotypically identical to plasma cell myeloma, but with osseous or extra-osseous localized growth pattern without evidence of systemic disease such as multiple myeloma (MM) (1).

Plasmacytoma is a malignant neoplasm of monoclonal B-cell proliferation and consists of three distinct entities according to the International Myeloma Working Group, 2003: solitary plasmacytoma of bone (SPB), extramedullary plasmacytoma (EMP) and multiple primary or recurrent plasmacytomas (2, 3). The EMP accounts for less than 4% of all plasma cell tumors and represents 1% of all head and neck (HN) tumors (4). Only a few cases of EMP (15%-20%) progress to MM (3) however, despite recent advances in the laboratory, imaging, and clinical evaluation, it is still impossible to identify which cases of EMP will progress to MM (5).

Biopsy of the tumor, based on the morphologic and immunophenotypic findings - localized monoclonal plasma cells without plasma cell proliferation in other sites in the absence of malignant lymphoma (5) - is required for the diagnosis. For instance, CD138 and CD38 are the most useful plasma cell markers (1, 6),

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whereas cytogenetic analysis FISH reveals specific chromosomal abnormalities, both translocation and deletions, with a prognostic value (2).

Although different therapeutic approaches are proposed in the literature, to date, radiotherapy (RT) represents the treatment of choice for EMP (2, 5). However, healthy tissues in the HN area are very sensitive to radiation, resulting in possible long-term sequelae. For these reasons, researchers are constantly searching for therapeutic options able to improve the precision of irradiation delivery to image-based targets and to spare non-involved critical tissue.

The CyberKnife® is a relatively new frameless robotic radiosurgery system (SRS) that combines a robotic arm with a linear accelerator, usually used for the treatment of brain metastases, soft tissue lesions and retreatment of HN cancers. Notwithstanding, the use of CyberKnife® as exclusive therapy for HN cancers, is relatively new. The system depends on a co-registration of digitally reconstructed radiographs generated from computer tomography (CT) images and X-ray projections that are captured during the treatment session (6). Changes in target position are transmitted to the robotic arm, which adjusts the pointing of the treatment beam, minimizing treatment errors associated with the patient positioning. CyberKnife® provides the administration of suitable doses precisely to the tumor, sparing normal surrounding tissue and critical structures such as the optic nerve, or carotid artery (7). Therefore lesions close to critical structures can be treated more effectively because of the rapid dose fall-off at the periphery, with an achieved local disease control of 83.8% (6).

To properly irradiate all local-regional EMP cells with doses sufficient for tumor control and to preserve as much healthy tissues as possible, we used, for the first time, a CyberKnife®-stereotactic radiotherapy (SRT) for the treatment of a sino-nasal EMP.

Case report

A 72-year-old man was admitted to the ENT Unit of "Federico II" University of Naples, Italy, complaining of right nasal respiratory obstruction and ipsilateral hematic discharge for three months. The patient gave informed, signed consent to participate in the study. Medical history revealed smoking habit, without any other significant risk factors. Nasal endoscopy showed a soft bloody tumor mass in the right nasal cavity. No palpable latero-cervical lymph

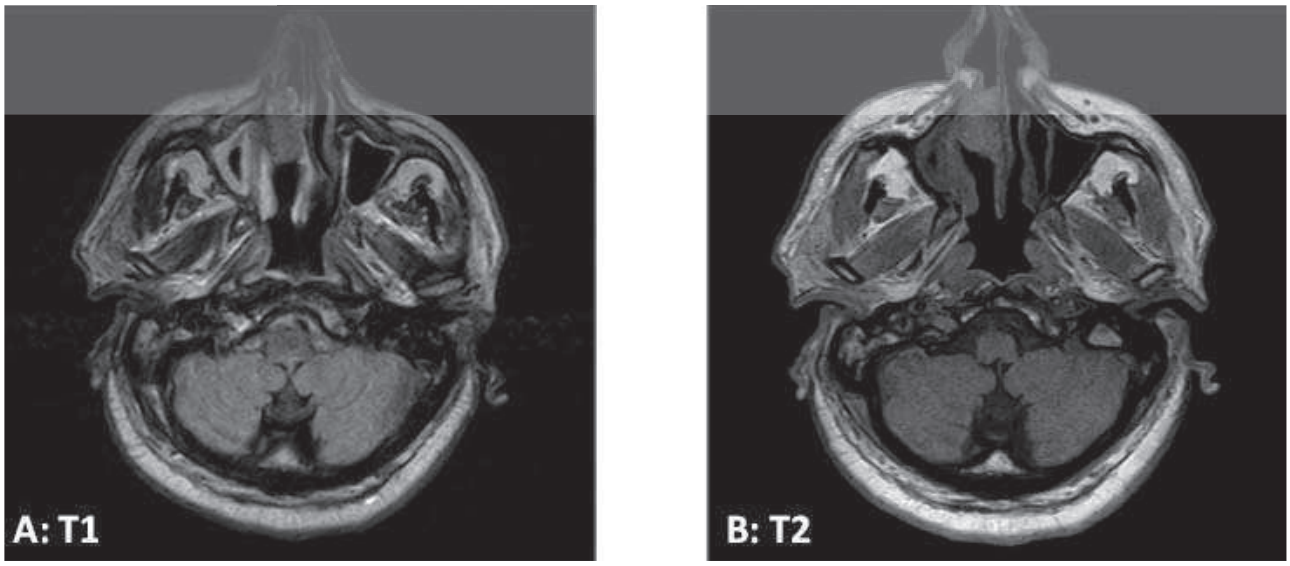

Fig. 1. *Magnetic resonance imaging (MRI) with contrast enhancement. MRI showed an ovoid formation of relatively hyperintense signal in T1 axial sequence (**A**) and of relatively hypointense signal in T2 axial sequence (**B**) in the right nasal cavity.*

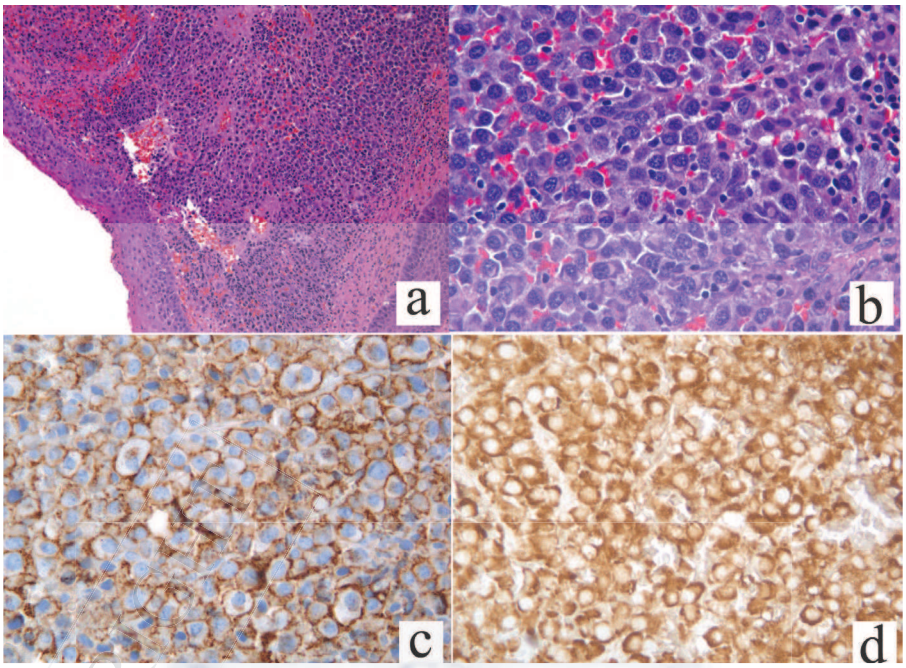

Fig. 2. *Immunohistochemical evaluation.* ***a)*** *The subepithelial corion was massively infiltrated by neoplastic cells with the typical plasma cell morphology (hematoxylin and eosin stain, 10x);* ***b)*** *neoplastic cells contained the typical Russel body that is a large, eosinophilic, homogeneous immunoglobulin-containing inclusion (hematoxylin and eosin stain, 40x); they were strongly and diffusely immunoreactive for CD138 (**c**) and for κ light chain (**d**).*

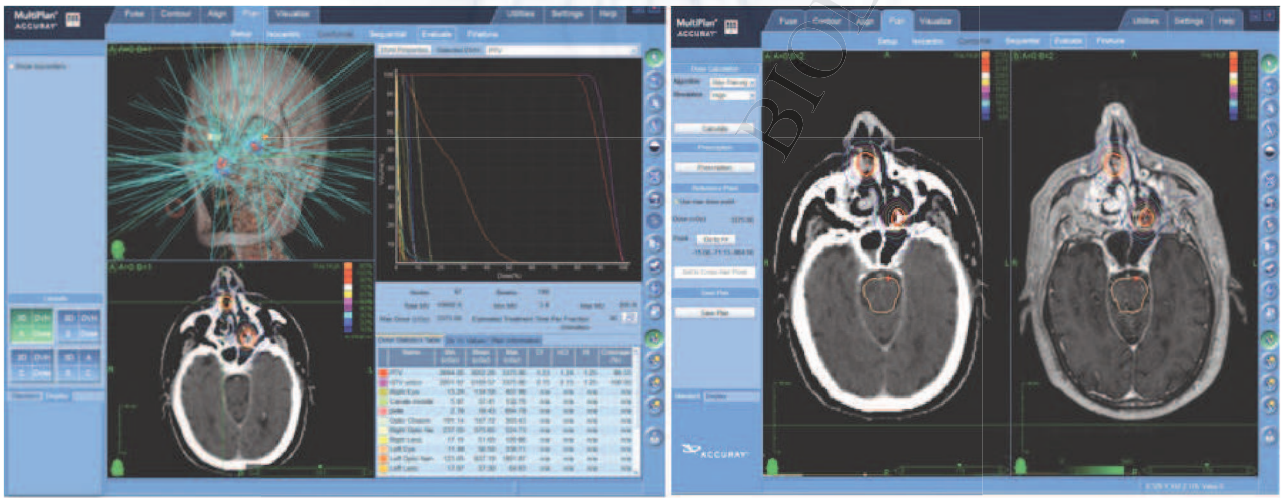

Fig. 3. *CyberKnife®-SRT. Contouring of target and organs at risk with simul-TC/MRI and DVH fusion images of treatment planning. The patient underwent CyberKnife® SRT with a total dose of 27 Gy at isodose line of 80% in 3 fractions.*

nodes were found. Monoclonal spike in serum, as well as monoclonal Bence–Jones protein in the urine electrophoresis, were absent. Renal, liver and blood profiles were normal. CT scan without contrast revealed the presence of soft tissue involving frontal, ethmoidal and maxillary right sinuses, extending into the ipsilateral nasal cavity. No bone erosion was observed. Magnetic resonance imaging (MRI) with contrast enhancement showed an ovoid formation of relatively hyperintense signal in T1 and FLAIR sequences and of relatively hypointense signal in T2 in the right nasal cavity (diameter 10 mm) (Fig. 1). The nasal biopsy, performed under local anesthesia, revealed the presence of a massive subepithelial corion infiltration of neoplastic cells with the typical plasma cell morphology. Immunohistochemical evaluation showed diffuse reactivity for CD138 and κ light chain, in the absence of λ light chain reactivity, characteristic of EMP (Fig. 2). Fluorescent in situ hybridization (FISH) cytogenetic analysis revealed the absence of del(13q14.3), del(17p13.1), t(11;14)(q13;q32) and t(4;14)(p16q32). The bone marrow needle biopsy did not show any skeletal involvement nor did the FDG-PET, that revealed increased activity in the right nasal cavity and left posterior ethmoid (SUV max 9.2, 10.3).

To preserve the critical structures (eyes, optic nerve, brainstem) the patient underwent SRT using the CyberKnife® VSI System (Accuray, Sunnvale, CA, USA) at a total dose of 27 Gy at isodose line of 80% in 3 fractions, carried out in the Radiotherapy Unit of the National Cancer Institute Pascale Foundation in Naples (Fig. 3). For the treatment planning we used Multiplan 4.6® (Accuray, Sunnvale, CA, USA) with Ray-tracing dose calculation algorithm. Cyberknife treatment parameters were as follows: PTV (GTV+2mm) volume: 5391 mm^3. The conformality index was 1.23 and the homogeneity index 1.25; PTV coverage of 99%; 199 beams, Iris Collimator (apertures 10,12.5, 15, 20, 25 mm), 6D_Skull Tracking Method and treatment time per fraction 40 minutes; the maximal dose to the left optic nerve was 1891 cGy and V1500 cGy was 39 mm^3, the maximal dose to the left eye was 338 cGy and the maximal dose to the optic chiasm was 303 cGy. The patient did not report any adverse event after treatment and showed a complete response to treatment 6 months after the CyberKnife®-SRT intervention. At 15 months follow-up, the patient was asymptomatic without recurrence. To the best of our knowledge this is the first case of sino-nasal EMP reported in the literature treated with CyberKnife®-SRT.

DISCUSSION

EMP is a rare plasma cell neoplasm which involves soft tissues, without systemic involvement attributing to MM. It may originate in many sites, although most frequently it occurs in the upper respiratory tract and oral cavity (1, 5).

Since EMP concerns diversified clinical and therapeutic features, the diagnosis of EMP and the treatment should be discussed by a multidisciplinary cancer board comprising the ENT surgeon, the onco-hematologist, the pathologist, and the radiation-oncologist.

EMP diagnostic procedures should comprise laboratory study (serum and urine protein electrophoresis, quantitative Ig and beta-2-microglobulin determination in serum), nasal endoscopic examination, extensive imaging study (CT, MRI, FDG-PET), biopsy and histological exam.

Furthermore, the bone marrow biopsy and aspiration, as well as the FISH cytogenetic analysis that reveals specific chromosomal abnormalities, both translocations and deletions, are of the utmost importance to determine the percentage of plasma cells (< 5%) (2). Chromosome 13 deletion is associated with a short disease-free as well as short global survival, whereas the deletion of chromosome 17p13 (locus of p53 gene) is associated with high risk of recurrence. In addition, t(4;14) is associated with a worse prognosis. In our case, the FISH cytogenetic analysis revealed the absence of del(13q14.3), del(17p13.1), t(11;14)(q13;q32) and t(4;14)(p16q32), suggestive of a better prognosis (2).

From a therapeutic point of view, according to the literature, the gold standard therapy for EMP is RT (5). Indeed, the solitary EMP <5 cm appears to have an excellent chance of local control with radiation doses in the range of 30-40 Gy in 10-20 fractions, whereas there is a higher risk of local failure in tumors >5 cm, which may require higher doses in

the range of 40-50 Gy (5). Cervical nodes should be included when involved (5). Overall, most studies report high local control rates of approximately 80-100% with moderate doses (8).

Although the role of chemotherapy in the treatment of EMP is quite controversial, it is considered only in patients with tumors >5 cm, high-grade tumors, refractory and/or relapsed disease, and in cases of progression to MM (2). However, the recent introduction of chemotherapeutic drugs (talidomide, lenalidomide and bortezomib), often in combination with dexamethasone, leads to the improvement of the overall and disease-free survival (6). Only in small, localized cases, complete surgical excision is appropriate (4).

Since HN plasma cell neoplasms can be very aggressive with a high tendency to recur locally, it is important to adequately irradiate all cancer cells with enough doses for tumor control (7). On the other hand, healthy tissues are very sensitive to radiation. For instance, salivary glands, larynx, constrictor muscles can be particularly damaged by radiotherapy resulting in long-term sequelae (skin toxicity, mucositis, xerostomia, dry-eye syndrome, radiation-induced retinopathy and neovascular glaucoma, lacrimal duct stenosis, brain necrosis and maxillary osteoradionecrosis) (6, 9). For these reasons, we believe that the ideal therapeutic protocol should preserve as much healthy tissue as possible and in this perspective CyberKnife®-SRT might represent an advantageous therapeutic strategy.

Taking into account the site of the lesion, the dimension and previous experiences with the Gammaknife and Cyberknife (9, 10), we chose for our patient a hypofractionated treatment in three fractions. Indeed, we achieved an excellent treatment plan with high target coverage and low-dose to the organs at risk, observing a complete therapeutic response without adverse effects (9).

In conclusion, due to the rarity, the site of occurrence, clinical history, the differential diagnosis with other inflammatory sinonasal diseases (11-14) the proximity of critical structures, as well as the long-time stable disease survival, we believe that the diagnostic approach to EMP should be multidisciplinary and the treatment considered case-by-case. However, although literature data confirmed radiotherapy as the therapy of choice (7, 4), to preserve the healthy surrounding tissue and critical structures, such as optic pathway or carotid artery, we propose CyberKnife®-SRT for the treatment of sinonasal EMP (6).

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