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CASE REPORT

C1–C2 pigmented villonodular synovitis and clear cell carcinoma: unexpected presentation of a rare disease and a review of the literature

José Pedro Lavrador · Edson Oliveira · Nuno Gil · António Fernandes Francisco · Sérgio Livraghi

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Abstract
Introduction Pigmented Villonodular synovitis (PVNS) is a rare vertebral pathology—around 50 reports, only 3 concerning C1–C2 location.
Case Report A 64-year-old man, submitted to a right nephrectomy for a clear cell carcinoma, presented with an asymptomatic osteolytic C1–C2 lesion. Even though the diagnosis of metastatic disease was the most probable, the presence of a solitary lesion without other osseous or systemic localization and the predicted low risk of recurrence imposed a surgical biopsy. A pigmented villonodular synovitis diagnosis was made, a rare vertebral pathology—around 50 reports, only 3 concerning C1–C2 location. No further treatment was assigned precluding the iatrogenic consequences of empirical treatments based on clinical diagnosis with no histopathological support. The patient remains stable at 18 months of follow-up.
Conclusion A large differential diagnosis should be made when the typical findings for metastatic disease are absent precluding the iatrogenic consequences of empirical treatments based on clinical diagnosis with no histopathological support.

Keywords Biopsy · Cervical spine · Clear cell carcinoma · Pigmented villonodular synovitis

J. P. Lavrador (✉) · E. Oliveira · A. F. Francisco · S. Livraghi
Neurosurgical Department, Hospital Santa Maria, Lisbon, Portugal
e-mail: jose.pedro.lavrador@gmail.com

N. Gil · S. Livraghi
Champalimaud Cancer Centre, Lisbon, Portugal

Introduction

The first report of pigmented villonodular synovitis (PVNS) was assigned to Jaffe et al. [15] and the first spinal report to Kleinman et al. [18]. It is a diffuse-type slow growing lesion related to villous or nodular overgrowth in the synovial epithelium with hemosiderin, non-encapsulated and intra-articular, belonging to the tenosynovial or synovial giant cell tumors and being its most frequent type (75 % of reported cases) [26]. The PVNS etiology, assumed as having a neoplastic nature, remains unknown besides the role that degenerative or metabolic diseases, inflammation and repetitive trauma and hemorrhages may assume [25]. This lesion is frequently found in knee and hip joints, its axial presentation being extremely rare [5]. To date, the last reviews indicate about 50 spinal synovial-type giant cell tumors in English literature [30]. With an estimated incidence is 1.8 case per million and a median age at presentation of 40 years, the PVNS spinal presentation reports have a slight female (57 %) and cervical (44 %) dominance [34]. The clinical symptoms can vary widely from pain due to monoarticular arthritis or structural spinal instability to radiculopathy or myelopathy, considering the mass location and size. The imagiological appearance on plain RX may show erosive bone changes and occasionally a definable soft tissue mass [6]; on CT, it is a hyperdense homogeneously enhancing soft tissue mass, rarely calcified; and on MRI has mixed signal intensity on T2-weighted images due to the presence of hemosiderin and hemorrhage [34]. This lesion is usually centered to the posterior elements of the vertebra, a disclosure from the literature regarding this issue [8]. There are four reported treatment options for spinal PVNS: surgery, radiation therapy, radioisotope infusion and conservative treatment with clinical and imagiological surveillance and symptomatic therapy. Concerning the paucity of cases, no studies were conducted to

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determine the results of each approach. Recurrence rates between 17 and 46 % were mentioned in the literature and some imply the DNA ploidy status and the proliferation index of tumor as possible reasons for this tumor behavior [25].

The authors report a cervical spine PVNS in a patient with a clear cell renal carcinoma background with a pre-operative diagnosis of a metastatic lesion, emphasizing the importance of a wide differential diagnosis and reviewing the PVNS clinical, imagiological and histological features and its treatment.

Case presentation

A 64-year-old man presented to neurosurgical outpatient consult for an osteolytic C1–C2 lesion. He had undergone a right nephrectomy 5 months earlier for a 61 mm lesion, discovered after ipsilateral mechanical lumbar pain complaint. The histopathology revealed clear cell carcinoma without angio or capsular invasion, grade 2 Furhman, classified a pT1bN0 stage. No further treatment was assigned. On a routine follow-up CT-scan, a right paratracheal nodule was detected. The evaluation was completed with a PET-CT 18FDG (18-fluorodeoxyglucose) confirming that nodule as ectopic thyroid tissue and presenting a previously unknown metabolically active C1 lesion with intense 18 FDG uptake, justifying a neurosurgical consult (Fig. 1).

The patient had unspecific mild cervicalgias present for years with no neurological compromise. A cervical spine MRI was made revealing an osteolytic lesion centered to C1 right lateral mass with extension to anterior arch and a soft tissue component regarding the pre-vertebral and latero-vertebral compartments and extension to C1–C2 right foramen and articulation, C2 right transverse process and lamina. It was hypointense in T1 and T2-weighted images with intense gadolinium uptake (Fig. 2). A cervical spine CT was made confirming the osteolytic nature of this lesion with cortical disruption (Fig. 3). Considering the clinical background and the imagiological features, the first diagnosis was in favor of a metastatic bone lesion. However, considering low probability of disease recurrence according to the SSIGN score, a biopsy was considered to appropriately identify the lesion.

A posterior cervical spine approach was performed to the C1–C2 region through a midline incision. After a careful exposure, a transosseous biopsy of right lateral mass and arch was made with several fragments achieved. The trajectory used was similar to C1 lateral mass screws with C-arm guidance. A small titanium marker was placed in the end of the biopsy path and a post-operative cervical CT showed the marker in the lesion (Fig. 4). No cervical instrumentation was performed as there were no clinical or imagiological instability signs. The wound was closured in the usual way. The patient recovered well and was discharged at day 3 post-operation.

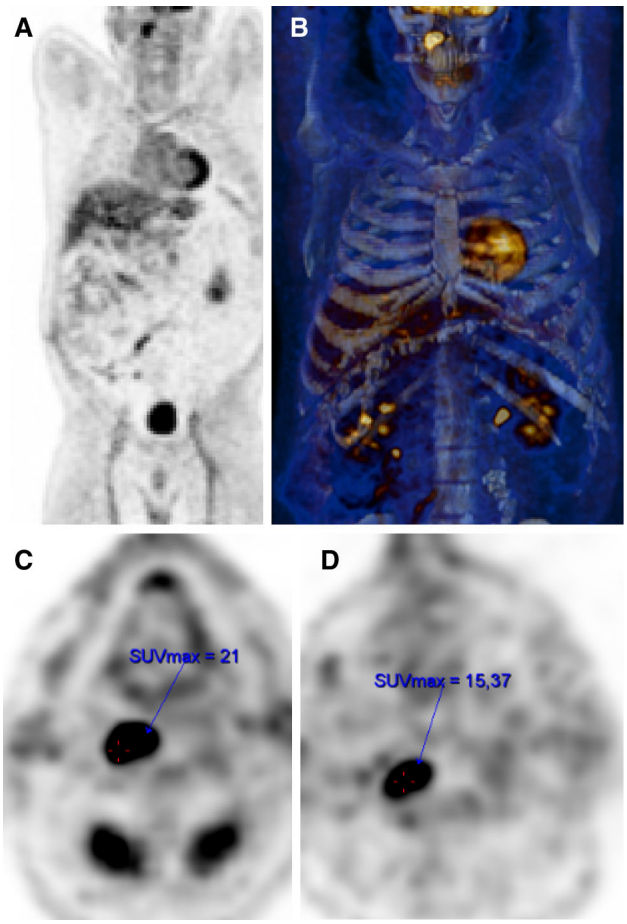

Fig. 1 PET-CT: abnormal and intense FDG uptake in the right half of anterior arch of atlas with and increase of maximum standardized uptake value (SUV)—15.37 to 21—in correlation with an apparent lytic lesion in CT

A histopathological diagnosis of PVNS was made (Fig. 5).

Concerning this asymptomatic lesion not related to patient's clinical oncological background, a conservative approach was decided and a clinical and imagiological surveillance was performed. After 18 months of follow-up, the patient has no clinical complaints concerning the cervical region. Imaging scans made at 3, 12 and 18 months are showing lesion stability and no changes in its imagiological features (Fig. 6).

Discussion

The PVNS diagnosis in a known oncological context demands a high level of suspicion. To our knowledge, this is the first report that documents this diagnosis in a patient with a previous known cancer.

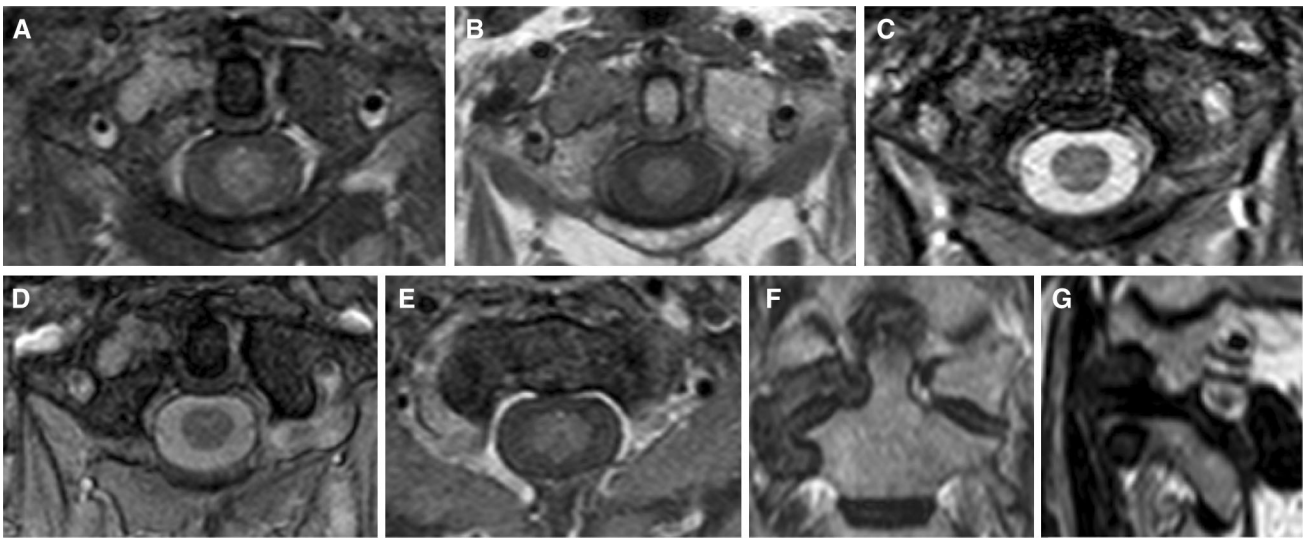

Fig. 2 **a** Axial T1W_TSE SPIR; **b** axial T1W_TSE;—hypointense lesion in T1 and (**c** axial T2W_FFE; **d** axial T2W_mFFE) hypointense in T2 concerning C1 right lateral mass with anterior cortical disruption (**e** axial T1W_TSE SPIR with gadolinium) and intense gadolinium uptake. **f** Coronal T2W_TSE and **g** sagittal T2W_TSE—extension of C1 lesion to C2 lateral mass and facets

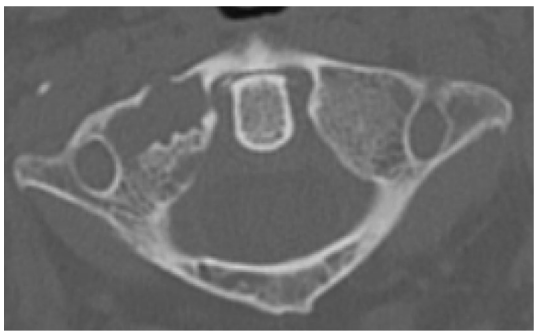

Fig. 3 Axial cervical CT—osteolytic lesion centered to right anterior mass, arch and facets with anterior cortical disruption

Osseous metastases occur in 50 % of patients with renal cell carcinoma; 15 % of these occur in the spine [19]. The presence of an osteolytic lesion in the cervical spine with homogenous contrast uptake on CT, MRI and PET-CT 18FDG should immediately raise the suspicious of a metastatic lesion. However, when considering the imagiological and topographic features of this lesion, there was no posterior vertebral body or pedicle involvement which is reported in some series as occurring in 99 and 60 % of metastatic spine disease, respectively [1, 34]. The fact that this was a solitary lesion also was against the metastatic origin and raised the question about the differential diagnosis.

In addition, the risk of recurrence was very low according to the SSIGN score (Postoperative Cancer Specific Survival following Radical Nephrectomy for Clear Cell Renal Cell Carcinoma) algorithm, which is a prediction model for patients with clear cell renal cell carcinoma treated with radical nephrectomy, developed by Frank et al. at the Mayo Clinic in 2002 [10]. This nomogram, later updated in 2005 [31] and externally validated in European [7] and Japanese patients [11], is based on the 1997 TNM classification, and uses primary tumor size, Fuhrman nuclear grade and tumor necrosis to classify the risk

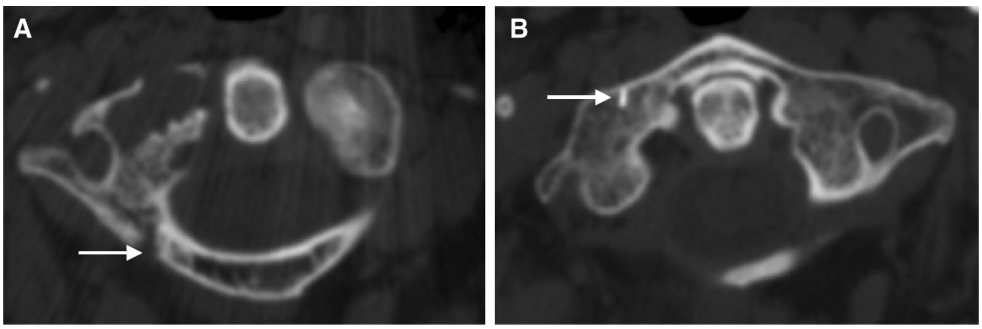

Fig. 4 Post-operation axial cervical CT—**a** (*arrow*) entry point; **b** (*arrow*) clip concerning the biopsy point

accordingly. In this particular patient, according to the SSIGN score, the estimated cancer-specific survival was 100 % at 1 year (with a 99.4 and 97.1 at 5 and 10 years, respectively), which meant that an alternative diagnosis would have to be considered.

Concerning the large size and the numerous spinal elements involved, other lesions should be considered in the differential diagnosis such as osteoblastoma, aneurysmal bone cyst, giant cell tumor of bone, chordoma, chondrosarcoma, and lymphoma [9, 14]. Osteoblastoma, chordoma and chondrosarcoma are not to be considered due to lack of mineralized matrix or calcification [4, 20, 29]. Microscopically, osteoblastoma differs from synovial-type giant cell tumors by featuring inter-anastomosing trabeculae of osteoid or woven bone bordered by a single layer of plump osteoblasts with no atypia and associated with a loose fibrovascular stroma and no foamy cells [20]; chordoma has small round nuclei and abundant vacuolated cytoplasm, described as physaliferous, but no giant cells [33]. Chondrosarcoma has increased cellularity, enlarged nuclei and patchy calcification areas [21]. An aneurysmal bone cyst is improbable due to the absence of cystic components with multiple fluid levels [24]. Histologically, it differs from PVNS by featuring cavernous, blood-filled spaces bordered by fibrous tissue with spindle cells, giant cells, and strands of bone or osteoid [12]. Giant cell tumor of bone is usually more anterior located [2] and has histologically a heterogeneous amount of mononuclear cells with round, oval or spindled nuclei with some giant multinuclear cells [12]. As well as with chordoma, chondrosarcoma displays high signal intensity on T2-weighted MR images because of their intrinsically high water content [29]. Concerning the smaller lesions beyond the synovial-based processes or related structures, gout, calcium pyrophosphate deposition, amyloid deposition, inflammatory arthropathy and synovial chondromatosis usually have intermediate-to-low signal on all MR pulse sequences related to chronicity and fibrosis similar to the intrinsic characteristics of spinal PVNS (except synovial chondromatosis) [23]. Nevertheless, their systemic component (for example chronic renal failure for amyloid deposition), the serum markers (as rheumatoid factor for inflammatory arthropathy) or their CT appearance (calcifications for calcium pyrophosphate deposition and synovial chondromatosis) are useful differential diagnosis. The PVNS diagnosis may be considered but due to its rarity, it should be among the less probable ones.

Regarding the differential diagnosis of a large lesion that seems to be an aggressive tumor, younger age, a solitary non-cystic lesion centered in the posterior elements, lack of mineralization and low-to-intermediate signal intensity on all MR pulse sequences may suggest the diagnosis of PVNS. Concerning the smaller lesions, as in our patient, a synovial-based lesion consisting in a solitary focus, lack of underlying disease or systemic arthropathy, no calcification as well as low-to-intermediate signal intensity on all MR images should raise the suspicious of PVNS. The diagnosis of PVNS was assigned due to the histopathological features of a nodular lesion composed of atypical cells in a sclerosing stroma with a villous pattern concerning a hyperplastic synovium. Regarding its cellular components, siderophages and xanthoma cells together with other inflammatory cells are dominant which explains its immunoreactivity to macrophage markers—CD68.

To our knowledge, even though the cervical spine location was the most common axial location—23 reported cases [3, 8, 12, 13, 16–18, 22, 27], only three case reports describes a lesion involving either C1 or C2 [8, 12, 27], and the others concern the subaxial cervical spine. In these cases, posterior elements involvement was documented in 87 % (20/23), although our patient showed a prominent paramedian anterior involvement, and the male:female ratio was ~1:1 (11/12). The treatment options described were gross total resection (GTR) in 56 % [follow-up of 13 patients: 69 % with no identifiable disease (ND), 15 % lost to follow-up (LFU), 17 % no available data (N/A)] biopsy (B) in 15 % (follow-up of 4 patients: 2 stable, 1 N/A and another LFU), incomplete resection (IR) followed for GTR

Table 1 Cervical spine PVNS treatment options and outcome

GTR: 56 % (13)	ND: 69 % (9)
	N/A: 16 % (2)
	LFU: 16 % (2)
B: 15 % (4)	Stable: 50 % (2)
	N/A: 25 % (1)
	LFU: 25 % (1)
IR + GTR + XRT: 9 % (2)	Stable: 50 % (1)
	ND: 50 % (1)
GTR + XRT: 9 % (2)	ND: 100 % (2)
B + GTR: 4 % (1)	ND (1)
IR: 4 % (1)	LFU (1)

B biopsy, *GTR* gross total resection, *IR* incomplete resection, *LFU* lost to follow-up, *N/A* non-available information, *ND* no evidence of disease, *XTR* external radiotherapy

Table 2 C1–C2 PVNS treatment options and outcome

Patient 1	GTR: ND at 11 years of follow-up
Patient 2	IR + GRT + XRT: residual tumor at 5 years of follow-up
Patient 3	B + stabilization procedure: stable disease at 2 years of follow-up
Patient 4 (present report)	B: stable disease at 18 months of follow-up

B biopsy, *GTR* gross total resection, *IR* incomplete resection, *ND* no evidence of disease, *XTR* external radiotherapy

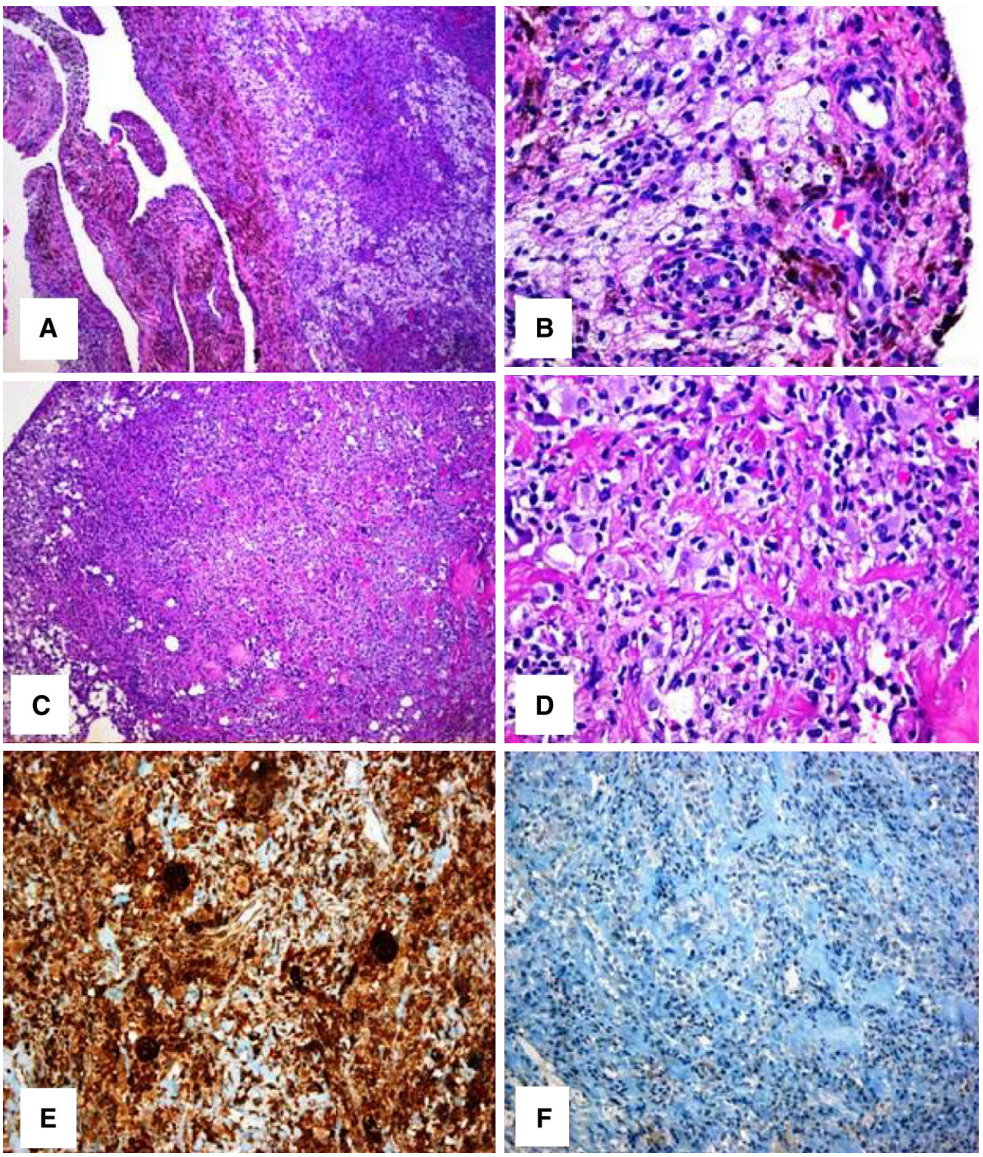

Fig. 5 Microscopic appearance of pigmented villonodular synovitis. **a** Low power view showing the villous appearance of the proliferation and hyperplastic synovium. **b** High power view showing an area with predominant foamy cells and hemosiderin-laden macrophages. **c** Low power view of a nodular lesion composed (**d**) of atypical cells in a sclerosing stroma. These cells are immunoreactive to the macrophage marker CD68 (**e**) and negative for the epithelial marker cytokeratin AE1/AE3 (**f**)

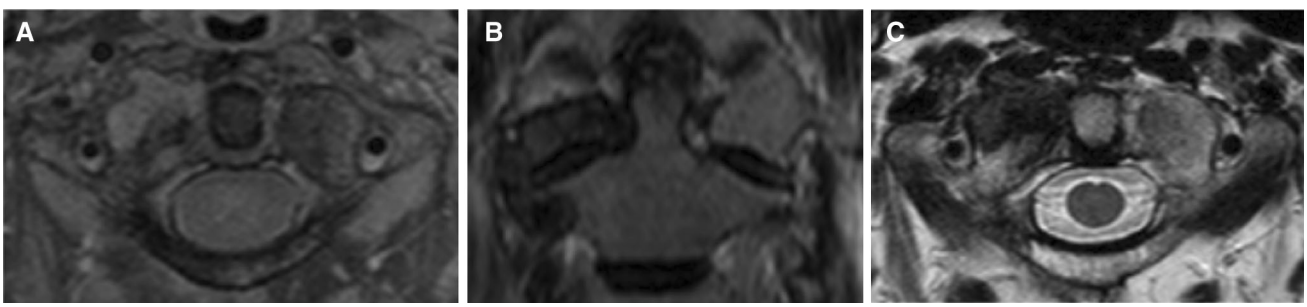

Fig. 6 18 months post-biopsy MRI—**a** axial T1W_SPIR with gadolinium, **b** coronal T2W_TSE and **c** axial T2W_TSE_DRIVE: stable C1–C2 right lateral mass, arch and facets lesion regarding its dimensions and imaging characteristics

and radiotherapy (XRT) in 9 % (follow-up of 2 patients: 1 stable and another with residual disease), GTR and XRT in 9 % (follow-up of the 2 patients: ND), B and GTR in 4 % (follow-up of the patient, ND) and IR alone in 4 % (follow-up of the patient, LFU) (Table 1). Concerning the reported cases regarding C1–C2 involvement, a GTR was performed in one patient with ND at 11 years of follow-up [27], IR followed by GTR and XRT was performed in another one with residual tumor at 5 years of follow-up [12], and in the last one a biopsy and stabilization was performed with stable disease at 2 years of follow-up [8] (Table 2).

In this clinical situation, a percutaneous procedure for such a high cervical level was deemed riskier by our neuroradiological colleagues than an open approach, which is supported by the few reports of this approach [32]. In terms of the likelihood of obtaining samples both in quantity and quality for reaching an accurate diagnosis, the surgical approach was also considered to be superior by the neuro-oncology multidisciplinary team, considering that cervical location was traditional associated with an increase in false negative results [28].

Concerning these data and considering the renal carcinoma as the main vital prognostic factor in our patient, a conservative clinical and imagiological follow-up and a symptom-control approach seemed an appropriate therapeutic approach.

Conclusion

PVNS is a rare spinal tumor. When considering a solitary vertebral lesion in a patient with a known solid organ cancer, the probability of its occurrence is even smaller. However, in those cases where the typical imagiological and topographical findings of spinal metastatic lesions are absent, this should be considered in differential diagnosis, precluding the consequences of empirical treatments based on clinical diagnosis with no histopathological support.

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Conflict of interest None of the authors has any potential conflict of interest.

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