knowledge about its duration and its influence on quality of life. Response is measured by two questionnaires: EORTC-QLQ-C15-PAL and the Brief Pain inventory (BPI). To date 27 out of 30 patients are accrued in this prospective study.

Conclusion

In conclusion, two-thirds of patients with local pain from pancreatic cancer experienced pain relief after a short course of palliative radiotherapy in our single institution retrospective study of 61 patients. No grade 3 or higher toxicity was observed. The prospective PAINPANC study is actively accruing.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

[1] De Angelis R, Sant M, Coleman MP, et al. EUROCARE-5 Working Group. Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE–5 – a population-based study. Lancet Oncol. 2014;15:23–34.
[2] Hidalgo M. Pancreatic cancer. N Engl J Med. 2010;362:1605–1617.
[3] Li D, Xie K, Wolff R, et al. Pancreatic cancer. Lancet. 2004;363:1049–1057.
[4] Bilimoria KY, Bentrem DJ, Ko CY, et al. Validation of the 6th edition AJCC Pancreatic Cancer Staging System: report from the National Cancer Database. Cancer. 2007;110:738–744.
[5] Yeo CJ. Pancreatic cancer: 1998 update. J Am Coll Surg. 1998;187:429–442.
[6] Bridenbaugh LD, Moore DC, Campbell DD. Management of upper abdominal cancer pain. JAMA. 1964;190:99–102.
[7] Yan BM, Myers RP. Neurolytic celiac plexus block for pain control in unresectable pancreatic cancer. Am J Gastroenterol. 2007;102:430–438.
[8] Eisenberg E, Carr DB, Chalmers TC. Neurolytic celiac plexus block for treatment of cancer pain: a meta-analysis. Anesth Analg. 1995;80:290–295.
[9] van Geenen RC, Keyzer-Dekker CM, van Tienhoven G. Pain management of patients with unresectable peripancreatic carcinoma. World J Surg. 2002;26:715–720.
[10] Morganti AG, Trodella L, Valentini V, et al. Pain relief with short-term irradiation in locally advanced carcinoma of the pancreas. J Palliat Care. 2003;19:258–262.
[11] Wolny-Rokicka E, Sutkowski K, Grządziel A, et al. Tolerance and efficacy of palliative radiotherapy for advanced pancreatic cancer: a retrospective analysis of single-institutional experiences. Mol Clin Oncol. 2016;4:1088–1092.
[12] Comito T, Cozzi L, Zerbi A, et al. Clinical results of stereotactic body radiotherapy (SBRT) in the treatment of isolated local recurrence of pancreatic cancer after R0 surgery: a retrospective study. Eur J Surg Oncol. 2017;43:735–742.
[13] Su TS, Liang P, Lu HZ, et al. Stereotactic body radiotherapy using CyberKnife for locally advanced unresectable and metastatic pancreatic cancer. Worl J Gastroenterol. 2015;21:8156–8162.
[14] Bernards N, Haj Mohammad N, Creemers GJ, et al. Ten weeks to live: a population-based study on treatment and survival of patients with metastatic pancreatic cancer in the south of the Netherlands. Acta Oncol. 2015;54:403–410.
[15] Nederlands trial register. [cited 2017 Nov 10]. Available from: http://www.trialregister.nl/trialreg/index.asp

LETTER TO THE EDITOR

Primary bone lymphoma presenting as skeletal lesions in a patient recently treated for prostate cancer

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Introduction

Secondary malignant dissemination to the bone is the most common site of metastatic tumor growth. Bone metastases are highly prevalent in breast and prostate cancer but also common in various other solid tumors [1]. For hematological malignancies the clinical spectrum ranges from no focal skeletal lesions in leukemia to lytic lesions as the hallmark of multiple myeloma. Pain and fatigue are common symptoms of bone metastases and inflict significant morbidity. More severe skeletal-related events (SRE) comprise pathologic fracture, spinal chord compression, radiotherapy and surgery to bone.

Independent of the presence or absence of bone metastases, androgen deprivation therapy (ADT) plays a significant role in inducing osteopenia and secondary SRE in patients treated for prostate cancer [2,3]. We report a case of severe skeletal pain in a patient recently treated for high-risk prostate cancer that highlights the importance of a persistent diagnostic strategy to detect a rare presentation of primary bone lymphoma.

Case presentation

A 65-year old man presented to the emergency department with a 2-weeks history of consistent pain in the lower part of the thoracic spine that increased with physical activity. The patient reported no previous trauma.

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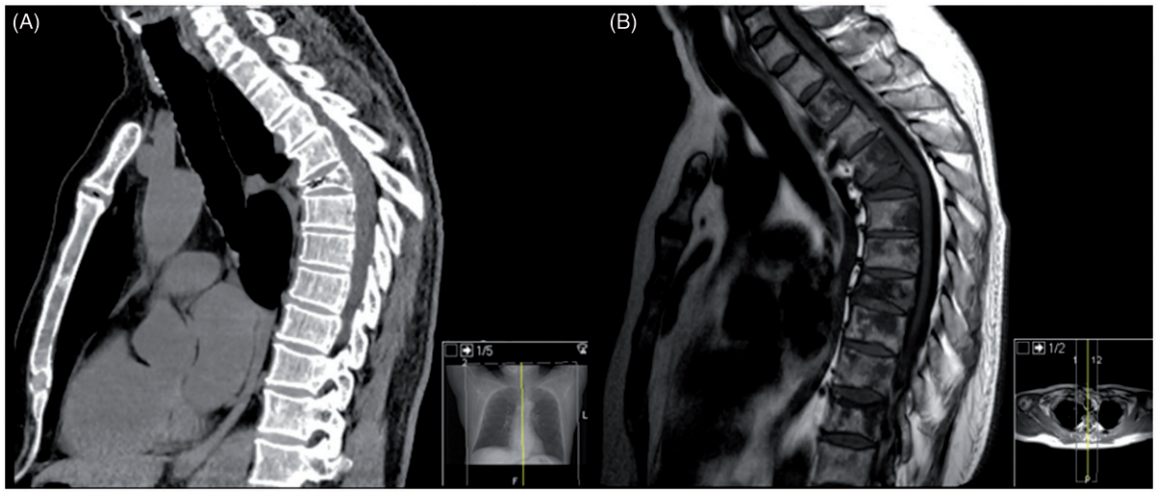

Figure 1. Comparison of imaging modalities. Computed tomography (CT) shows the compression fracture of Th5 but fails to visualize extensive primary bone lymphoma lesions in the thoracic spine detectable on MRI. (A) CT sagittal reconstruction without iv contrast. (B) T1-weighted sagittal MRI. Patient information and technical details were removed and images were cropped and scaled to similar frames but not changed otherwise.

One year earlier the patient had been diagnosed with high-risk prostate cancer, T3b, Gleason $4+3=7$ with an extensive grade 4 component. The initial serum PSA was 60 μg/l. MRI of the pelvis showed a multifocal tumor, which infiltrated the whole prostate with bilateral invasion of the vesicular glands. No pathologic lymph nodes were detected. MRI and bone scintigraphy did not show any signs of bone metastases.

The patient was treated with total androgen blockade (leuprorelin 11.25 mg s.c. and bicalutamide 50 mg daily) for 3 months before and during intensity-modulated radiation therapy (IMRT) up to 72.5 Gy to the prostate and vesicular glands and 52.2 Gy to locoregional lymph nodes. We initiated adjuvant treatment with bicalutamide 150 mg daily that was ongoing at the time of presentation to the emergency department. The patient had previously been healthy except for mild peripheral sensory neuropathy of unknown origin that was investigated approximately 8 years prior to developing prostate cancer.

The patient has a brother with prostate cancer but otherwise no family history of cancer. He is a non-smoker with a low consumption of alcohol.

The physical examination in the emergency room showed no tenderness over the spinal column. Blood work was within reference intervals except for grade 1 anemia (hemoglobin 108 g/l) and a CRP increase to 28 mg/l. Serum PSA was 0.07 μg/l. A CT scan demonstrated a vertebral compression fracture of Th5 that was considered to be benign. The patient received pain medication with NSAID and was referred to a physiotherapist. His mild anemia and increased CRP did not warrant any further intervention and the patient was referred to his primary care physician for follow-up. Symptoms improved initially but relapsed quickly with severe pain in the back and mild muscle weakness in the lower extremities. CRP increased successively to 145 mg/l and LDH increased to 8.3 μkat/l. A second CT scan 7 weeks after the first examination showed progression of the vertebral compression and a minor degree of impact upon the spinal canal. The patient received increased pain medication and was started on high-dose steroids. A CT-guided biopsy of the lesion was performed, which showed hemorrhage without the presence of malignant cells. The results were interpreted as a benign vertebral compression fracture probably secondary to ADT. We continued conservative therapy, tapered steroids and planned a follow-up MRI after six to eight weeks if symptoms did not improve.

Just a few weeks later, while traveling abroad, the patient was admitted to a hospital with deteriorating symptoms. He had new symptoms in the form of fever up to 39.5 °C and night sweats despite the ongoing steroids. A third CT scan showed once again collapse of Th5 but a complementary MRI of the spine revealed extensive metastatic disease in several vertebrae that was not evident on any of the CT scans. A new core biopsy of L4 was performed. The biopsy was consistent with fibrosis and new bone formation without any signs of malignancy. None of the radiological exams showed any sign of pathologically enlarged lymph nodes or visceral metastases (Figure 1).

Upon returning to Sweden, a repeat MRI showed vertebral compression of Th5, Th8, Th11 and L4 with tumor growth in the whole axial skeleton. An open bone biopsy was planned. The biopsy was delayed because the patient was hesitant towards new sampling after the previous extensive diagnostic procedures. We initiated a myeloma work-up [4] that was negative for monoclonal protein in serum or urine. Bone marrow aspiration and biopsy showed a mature population of white cells with a normal ratio of neutrophil granulocytes, lymphocytes, and monocytes. Flow cytometry revealed no pathologic cell populations. Less than 5% sideroblasts and no ring sideroblasts were observed and the patient had normal serum ferritin and triglyceride levels. At this time, the patient developed increasing muscle weakness and sensory neuropathy and was admitted to the department of neurology for work-up. Screening for paraneoplastic antibodies was negative and a neurophysiological examination gave inconclusive results. Due to impending spinal chord compression,

the patient underwent an acute laminectomy of Th5. At first, morphological assessment of tissue fragments was not possible due to artifacts. Epithelial markers (i.e., CK, AE1/AE3) were negative and only background signals for androgen receptor, PSA and PSMA were observed. A separate tissue block was decalcified and results were pending while the patient continued to deteriorate. Finally, a diagnosis of a highly malignant B-cell lymphoma could be made based on the morphological finding of a dedifferentiated tumor in the decalcified material. Lymphoma cells expressed high grades of CD20 but subtyping proved to be impossible because of the long decalcification process.

The patient was immediately referred to the department of hematology. Additional staging by PET/CT showed as expected tracer uptake in the spine, costae, sternum, pelvis, proximal extremities, the skull base and mandible but also pathological uptake in a 5 mm (short axis) lymph node in the right groin. No other lesions were found. Analysis of the cerebrospinal fluid (CSF) did not show a clonal B lymphocytic population. The lymphoma was classified as a primary bone diffuse large B-cell lymphoma (DLBCL). The patient received six cycles of R-CHOEP14 and intrathecal methotrexate that was relatively well tolerated. Follow-up PET/CT after six cycles showed a complete remission. The patient is currently recurrence free six months after treatment for DLBCL and has a PSA < 0.01 μg/l. He still experiences significant bone pain that requires medication with opioids, bisphosphonates and a support corset.

Discussion

Our initial concern was to assess a possible recurrence of the patient's prostate cancer. The patient met all criteria for high-risk prostate cancer according to the D'amico classification and was treated according to a slightly intensified SPCG-7 protocol [5]. In this group 10-years biochemical relapse-free survival is 74.1%, but we estimated the patient had a substantially higher individual relapse-risk because of high serum PSA and extensive tumor growth. PSA-negative prostate cancer is rare, usually reported at $<1\%$ of patients, and highly unlikely in this patient who initially presented with high PSA levels [6].

To assess other causes of the single bone lesion on CT scan, we prioritized a biopsy that was consistent with an osteoporotic vertebral compression fracture. Normally men lose BMD at a rate of approximately 0.5–1.0% yearly starting in middle age but the rate increases to 4.6% and 3.9% at the lumbar spine and the femoral neck, respectively, if treated with ADT for one year. Significant changes are evident as early as 6 months after ADT initiation [3] and were considered the cause of the patient's Th5 fracture.

Current practice for vertebral compression does not recommend imaging modalities other than CT [7] but suboptimal sensitivity of CT proved to be a major shortcoming in the initial diagnostic approach. Literature reports a sensitivity of only 74% for osteolytic and 56% for osteosclerotic metastases with CT and a specificity of 56%. MRI and PET/CT have a sensitivity of 97% and 100%, respectively, and a similarly good specificity [8].

When we detected multiple metastatic lesions and the patient started to show B symptoms we suspected a hematological malignancy. Multiple myeloma was ruled out by bone marrow aspiration and biopsy and lack of monoclonal protein in serum and urine. Bone marrow and serum tests did not show signs of hemophagocytic lymphohisticytosis. A neurological paramalignancy work-up returned negative results. Of note, paraneoplastic syndromes that could have explained the patient's symptoms are extremely rare in lymphomas [9] and we now consider them secondary to reduced performance status, high levels of inflammation and spinal chord compression.

The diagnosis of primary bone lymphoma (PBS) could only be made after a fourth tissue sample through laminectomy had been obtained and a sufficient amount of tissue was available. The importance of sufficient biopsies is highlighted in the guidelines for lymphoma management but was difficult because no extra-osseous lesions had been detected [10]. DLBCL is the most common subtype of non-Hodgkin lymphoma (NHL) accounting for 30–40% of all cases. Bone marrow involvement is relatively common in NHL and can be detected in about 20–30% of patients. DLBCL is the dominant subtype in these patients [11,12]. PBL, in contrast, is extremely rare making up only 7% of primary malignant bone tumors, 5% of extranodal lymphomas, and $<1\%$ of NHL [12].

The patient received intensified treatment for his DLBCL and went into complete remission. We have currently no signs of a recurrence of his prostate cancer. However, the unusual diagnostic difficulties in this case contributed to a delay that inflicted extensive skeletal damage. The patient still experiences significant morbidity that only improves slightly with conservative treatment including external brace- and physiotherapy, bisphosphonates and pain medication.

Conclusion

The case highlights the importance of multimodal radiologic assessment and insistence on a histopathologically verified diagnosis. In this case, persistent sampling and repeated pathology were crucial to administer curative treatment despite prolonged and previously inconclusive work-up for metastatic disease.

Disclosure statement

The authors report no conflicts of interest. We declare no sources of funding for this report.

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References

[1] Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res. 2006;12: 6243s–6249s.

[2] Rizzoli R, Body JJ, Brandi ML, et al. Cancer-associated bone disease. Osteoporos Int. 2013;24:2929–2953.
[3] Maillefert J, Sibilia J, Michel F, et al. Bone mineral density in men treated with synthetic gonadotropin-releasing hormone agonists for prostatic carcinoma. J Urol. 1999;161:1219–1222.
[4] Dimopoulos M, Kyle R, Fermand JP, et al. Consensus recommendations for standard investigative workup: report of the international myeloma workshop consensus panel 3. Blood. 2011;117:4701–4705.
[5] Widmark A, Klepp O, Solberg A, et al. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. Lancet. 2009;373:301–308.
[6] Birtle AJ, Freeman A, Masters JR, et al. Clinical features of patients who present with metastatic prostate carcinoma and serum prostate-specific antigen (PSA) levels < 10 ng/mL: the "PSA negative" patients. Cancer. 2003;98:2362–2367.
[7] Alexandru D, So W. Evaluation and management of vertebral compression fractures. Perm J. 2012;16:46–51.
[8] O'Sullivan GJ, Carty FL, Cronin CG. Imaging of bone metastasis: an update. World J Radiol. 2015;7:202–211.
[9] Graus F, Ariño H, Dalmau J. Paraneoplastic neurological syndromes in Hodgkin and non-Hodgkin lymphomas. Blood. 2014;123:3230–3238.
[10] Tilly H, Gomes da Silva M, Vitolo U, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl 5):v116–v125.
[11] Conlan MG, Bast M, Armitage JO, et al. Bone marrow involvement by non-Hodgkin's lymphoma: the clinical significance of morphologic discordance between the lymph node and bone marrow. Nebraska lymphoma study group. J Clin Oncol. 1990;8:1163–1172.
[12] Wu H, Bui MM, Leston DG, et al. Clinical characteristics and prognostic factors of bone lymphomas: focus on the clinical significance of multifocal bone involvement by primary bone large B-cell lymphomas. BMC Cancer. 2014;14:900.

LETTER TO THE EDITOR

Non-cirrhotic portal hypertension associated with multicentric Castleman's disease: a case report

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Introduction

Idiopathic multicentric Castleman's disease (iMCD) is a rare polyclonal lymphoproliferative disorder. It is characterized by systemic inflammatory symptoms, cytopenias and multi-organ dysfunction caused by proinflammatory cytokines [1]. Even though hepatosplenomegaly and ascites are frequently associated with iMCD [1], portal hypertension appears to be infrequent [2]. Nodular regenerative hyperplasia (NRH) of the liver is also an unusual condition, which is characterized by a generalized benign transformation of the hepatic parenchyma into small regenerative nodules, with minimal or absent perisinusoidal or periportal fibrosis [3]. NRH is known to be associated with autoimmune, infectious, neoplastic, toxic and hematological conditions. It is usually asymptomatic, unless (non-cirrhotic) portal hypertension develops – estimated in 50% of the cases [3]. NRH in iMCD patients has only seldom been reported [4,5]. We present a case of iMCD with portal hypertension and pathological features of NRH.

Case report

A 32-year-old male patient was diagnosed with Castleman's disease (hyaline-vascular variant) in 2007. At that time, the patient presented with supraclavicular and mediastinal lymphadenopathies, without systemic symptoms and no active disease criteria. His medical history included a mild congenital factor V deficiency, without bleeding diathesis, and depressive and anxiety disorders for which he was medicated with escitalopram 20 mg id, olanzapine 10 mg id and lorazepam 2.5 mg id. There was no history of alcoholism. His family history was significant for scrotal cancer in his father.

Two years later, at age 34, the patient developed constitutional symptoms, consisting of malaise, anorexia, night sweats and weight loss, as well as epigastric pain. He weighted 70 kg, was afebrile, with normal blood pressure and heart rate. On physical examination, he had splenomegaly, but hepatomegaly, ascites and peripheral lymphadenopathy were absent. His laboratory evaluation revealed mild thrombocytopenia (118×10^9/L), elevated erythrocyte sedimentation rate (84 mm/h) and C-reactive protein (3.26 mg/dL). Liver enzymes were raised: aspartate aminotransferase 58 U/L (normal lower than 45 U/L); alanine aminotransferase 75 U/L (normal lower than 35 U/L); gamma-glutamyl transferase 237 U/L (normal lower than 55 U/L); and alkaline phosphatase 457 U/L (normal range 30–120 U/L). Polyclonal hypergammaglobulinemia and positive antinuclear antibodies (1:160) were also present. Bilirubin, lactate dehydrogenase, total proteins and albumin were normal.

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