

The Diagnostic Hurdle of an Elderly Male with Bone Pain: How ¹⁸F-FDG-PET Led to Diagnosis of a Leiomyosarcoma of the Adrenal Gland

HANNEKE W.M. VAN LAARHOVEN¹, MAARTEN VINKEN², ROEL MUS³,
UTA FLUCKE⁴, WIM J.G. OYEN² and WINETTE T. VAN DER GRAAF¹

*Departments of ¹Medical Oncology, ²Nuclear Medicine, ³Radiology and ⁴Pathology,
Radboud University Nijmegen Medical Centre, The Netherlands*

Abstract. It is uncommon for patients to present with bone metastases while the primary tumor is still unknown. The case of a patient with bone metastases as primary presentation of leiomyosarcoma, who was diagnosed after a ¹⁸F-FDG PET-CT and a CT-guided biopsy of the adrenal gland is described. If after routine physical, laboratory and radiological investigations no diagnosis can be made, ¹⁸F-FDG PET should be added to the conventional work-up of patients with unknown primary cancer. In this way, unnecessary and enduring suffering of symptomatic patients may be prevented.

The skeleton is a well-known site for metastases of several types of cancer and hematological malignancies (1). Of all newly diagnosed malignancies, the primary site is unknown in at least 2-5% of the cases and in only a few cases are the metastases located in the bone at initial clinical presentation (2, 3). Although in the majority of patients presenting with skeletal metastasis the lung (4) is identified as the primary tumor site, followed by the prostate and the breast, a variety of other malignancies have been described. In general, prognosis of unknown primaries is poor and doctor's delay in obtaining a diagnosis is not uncommon. Here, a case is presented of a patient with bone metastases at initial presentation who was diagnosed with metastatic leiomyosarcoma of the adrenal gland only after positron-emission tomography and computed tomography (PET-CT) and guided histological biopsy were performed.

Case Report

A 78-year-old male was referred from another hospital to the Department of Medical Oncology of the Radboud University Nijmegen Medical Centre because of suspected bone metastases. Four months previously he had experienced a sudden pain in his left hemithorax. Further analysis with a bone scintigraphy, a CT scan of the thorax and abdomen and an magnetic resonance image (MRI) of the spine were suggestive of bone metastases. Two random biopsies of the posterior iliacal crests showed myelofibrosis, but no malignancy. A biopsy of a painful rib did not reveal any abnormalities. The consulted pulmonary physician had no indication of a primary lung malignancy, neither on CT nor after bronchoscopy.

Upon presentation in the hospital, the patient complained of pain in his back, thorax and left scapula. In nine weeks, he had lost 16 kg of weight. His previous medical history consisted of constipation and pyrosis for eight years, diabetes type 2, hypertension, stenosis of the aortic valve and chronic bronchitis. His medication comprised metformine, acetyl salicylic acid, lisinopril, hydrochlorothiazide, irbesartan, a statin, omeprazole, terbutaline inhalations, acetaminophen and a non-steroidal anti-inflammatory drug. He had at least 20 pack years and consumed four alcoholic beverages a day. On physical examination, his blood pressure was 170/50 mm Hg and he had a systolic murmur matching the known aortic valve stenosis. On examination of the lungs, a prolonged expirium and basal rhonchi were heard. No abdominal abnormalities were found, except for an enlarged prostate at rectal examination.

Laboratory examination showed hemoglobin 7.8 mmol/L (normal values 8.5-11.0 mmol/L), and gamma-glutamyl transpeptidase 63 U/L (normal value <50 U/L), but otherwise no abnormalities. There was no M-protein; Bence Jones protein in the urine was negative; PSA was 2.5 µg/l and CA19.9 was 13 E/ml (both normal). A CT

Correspondence to: Hanneke W.M. van Laarhoven, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands. Fax: +31243540788, e-mail: h.vanlaarhoven@onco.umcn.nl

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of the thorax and abdomen showed multiple osteolytic lesions in the thoracic and abdominal skeleton, an enlarged left adrenal gland and an enlarged prostate. A hypodense lesion in the tail of the pancreas was present and a few lesions in the lungs were suspect for lung metastasis. The consulted urologist diagnosed benign prostate hyperplasia. A CT-guided biopsy of a lesion in the left iliacal bone was performed, which showed spindle cells, but no classifying diagnosis could be made. A PET-CT was performed which revealed multiple lesions in the spine, pelvis, femora, humeri and ribs. Focally high fluorodeoxy-glucose (FDG) uptake was observed in the left adrenal gland and the tail, head and corpus of the pancreas (Figure 1). A CT-guided biopsy of the left adrenal gland was performed. Histology showed spindle cells strongly positive for vimentin, smooth muscle cell isoform 1 and muscle-specific actin (Figure 2); S100 and pankeratin were negative. Based on these immunohistochemical results, six months after initial presentation, a diagnosis of leiomyosarcoma was made.

In the course of the diagnostic process, the patient's general condition deteriorated further, which made the commencement of any systemic treatment beyond scope. Because of increasing back pain, two weeks after diagnosis he was referred for radiation therapy of the thoracic spine. One week later he complained of weakness of his left arm and leg. A CT scan showed multiple brain metastases. Dexamethasone was started, unfortunately without much improvement. The patient died 11 days later.

Discussion

Bone pain in elderly patients might have several causes of which osteoporotic fractures and skeletal metastases are the top two probable diagnoses. Given the clinical and radiological presentation of the patient, bone metastases were highly suspected, and, based on the history of more than 20 pack years and the enlarged prostate on physical examination and CT, it was more than likely that the patient would be diagnosed with either primary lung or prostate cancer. However, thorough examination showed no evidence of a primary tumor in these organs and only after PET-CT and biopsy of a mesenchymal metastasis could the ultimate diagnosis, metastasized leiomyosarcoma of the adrenal gland, be made.

Leiomyosarcoma is a rare malignant tumor that originates from smooth muscle cells. In general, the incidence of bone metastases from soft tissue sarcoma is low, approximately 7%, and routine bone scanning in the work-up of asymptomatic patients is not recommended (5). Bone metastases as a presenting symptom of leiomyosarcoma are extremely rare. Nine other cases with osseous metastases as presenting manifestation of leiomyosarcoma have been reported in the

literature and have been reviewed by Elhammday *et al.* (6). All patients were relatively young (mean age 50 years) and the metastases tended to involve only one spinal level at the time of diagnosis. In contrast, the patient in this report was much older and the disease had spread extensively. The aberrant course of the disease in the patient is also illustrated by the development of brain metastases, which is uncommon for leiomyosarcoma (7). Moreover, the most common primary localizations of leiomyosarcoma are the uterus, gastrointestinal tract, retroperitoneum and subcutaneous tissue of the extremities. In this case, the most obvious site of origin was the adrenal gland. Only a few cases of primary leiomyosarcoma of the adrenal gland have been described, as summarized by Mohanty *et al.* (8). Alternatively, the pancreas may have been the primary site of origin (9). However, the different loci of increased FDG uptake within the pancreas suggest that in this patient, the pancreas was a metastatic site rather than the primary tumor site. The presentation and clinical course of this patient underscores the heterogeneity of leiomyosarcoma (10).

Once again, this case stresses the importance of obtaining adequate material for histological diagnosis. However, on the basis of biopsies of the suspected skeletal metastases alone, it was not possible to obtain a classifying diagnosis. Previous cases have also shown that histological analysis of bone metastases of unknown primary tumors seldom identifies the primary lesion (2, 11). Therefore, before turning to a skeletal biopsy, other lesions that are easier to approach should be sought. In this case, it was decided to attempt a guided skeletal biopsy first, as on CT the distinction between a malignant and benign cause of enlargement of the adrenal gland could not be made (12). The lesion in the tail of the pancreas was difficult to approach and was deemed benign on CT.

When performing biopsies of suspected bone metastases some caveats have to be taken into consideration: first, a multiple myeloma should be ruled out by laboratory testing; second, renal cell carcinoma should be deemed unlikely as these lesions are highly vascular (or embolisation before biopsy should take place); third, in cases of a single metastasis for which a curative resection is still optional, contamination of surrounding tissue due to the biopsy should be avoided (11).

In cases where standard physical and radiological investigations, including CT of thorax and abdomen, do not lead to a diagnosis, ¹⁸F-FDG PET should be part of the diagnostic work-up of patients with unknown primary cancer (11, 13, 14). It has been shown that PET and PET/CT can hence help localize the primary tumor in approximately 40% of all cases (15). When doing so, unnecessary delays in the diagnostic work-up are prevented, facilitating adequate and timely treatment of patients.

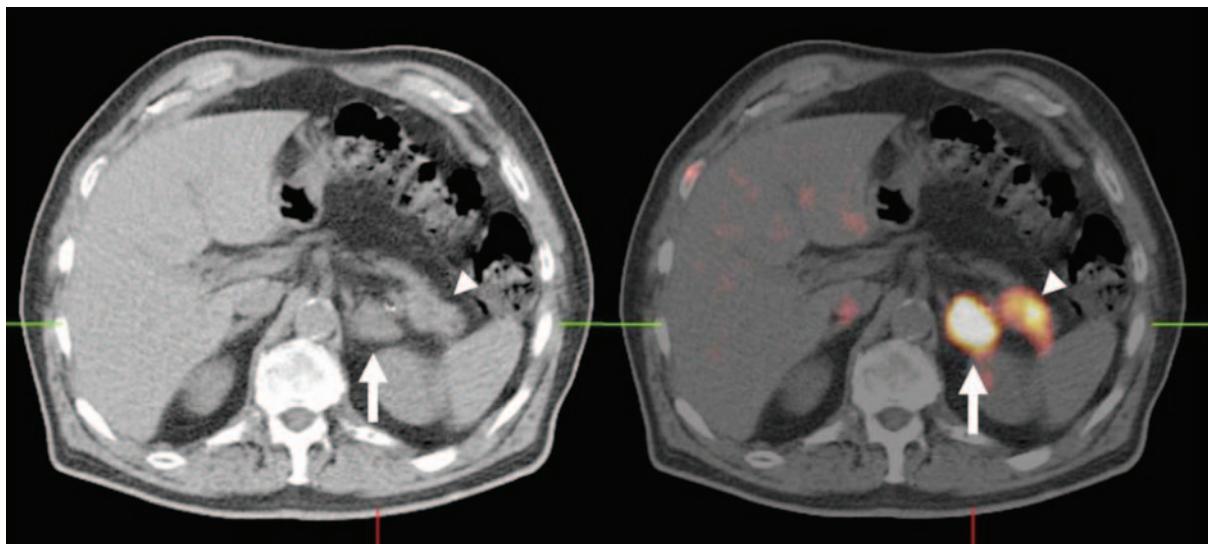


Figure 1. Transverse low-dose CT (left) and PET-CT images (right). Increased FDG accumulation can be seen in the enlarged left adrenal gland (arrow), as well as in the tail of the pancreas (arrowhead).

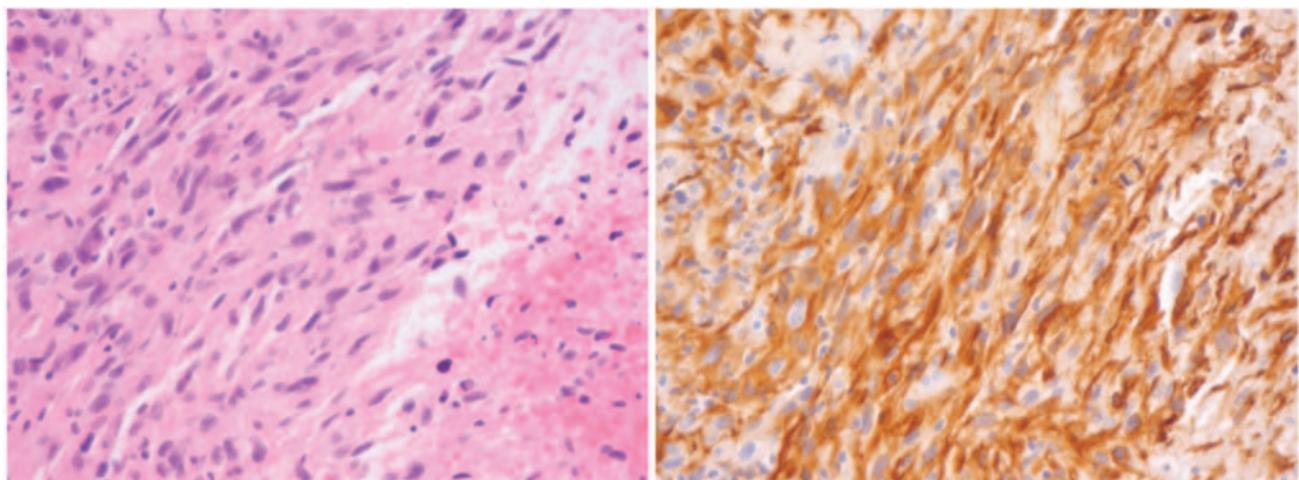


Figure 2. H&E staining of the biopsy of the adrenal gland, showing malignant spindle cell neoplasm (left). Expression of smooth muscle actin (right) indicated a leiomyomatous differentiation (magnification $\times 20$).

In conclusion, bone metastases as a presenting symptom of cancer are uncommon. Although common tumors such as lung, prostate and breast cancer are often the origin of bone metastases, rare primary tumors, as in the presented case of leiomyosarcoma, may be found. Therefore, it is essential to obtain a histological diagnosis. As bone biopsies often remain inconclusive, besides a diagnostic CT, an ^{18}F -FDG PET scan should be included in the work-up in time to identify lesions that can be biopsied more easily.

References

- 1 Buijs JT and van der PG: Osteotropic cancers: From primary tumor to bone. *Cancer Lett*, 2008.
- 2 Katagiri H, Takahashi M, Inagaki J, Sugiura H, Ito S and Iwata H: Determining the site of the primary cancer in patients with skeletal metastasis of unknown origin: a retrospective study. *Cancer* 86: 533-537, 1999.
- 3 Pimiento JM, Teso D, Malkan A, Dudrick SJ and Palesty JA: Cancer of unknown primary origin: a decade of experience in a community-based hospital. *Am J Surg* 194: 833-837, 2007.

- 4 Nottebaert M, Exner GU, von Hochstetter AR and Schreiber A: Metastatic bone disease from occult carcinoma: a profile. *Int Orthop* 13: 119-123, 1989.
- 5 Jager PL, Hoekstra HJ, Leeuw J, van Der Graaf WT, de Vries EG and Piers D: Routine bone scintigraphy in primary staging of soft tissue sarcoma: Is it worthwhile? *Cancer* 89: 1726-1731, 2000.
- 6 Elhammady MS, Manzano GR, Lebwohl N and Levi AD: Leiomyosarcoma metastases to the spine. Case series and review of the literature. *J Neurosurg Spine* 6: 178-183, 2007.
- 7 Honeybul S and Ha T: Leiomyosarcoma of the uterus metastatic to the brain: a case report. *Arch Gynecol Obstet*, 2008.
- 8 Mohanty SK, Balani JP and Parwani AV: Pleomorphic leiomyosarcoma of the adrenal gland: case report and review of the literature. *Urology* 70: 591-597, 2007.
- 9 Aihara H, Kawamura Y, Toyama N, Mori Y, Konishi F and Yamada S: A small leiomyosarcoma of the pancreas treated by local excision. *HPB (Oxford)* 4: 145-148, 2002.
- 10 Skubitz KM and D'Adamo DR: Sarcoma. *Mayo Clin Proc* 82: 1409-1432, 2007.
- 11 Rougraff BT, Kneisl JS and Simon MA: Skeletal metastases of unknown origin. A prospective study of a diagnostic strategy. *J Bone Joint Surg Am* 75: 1276-1281, 1993.
- 12 Quayle FJ, Spitler JA, Pierce RA, Lairmore TC, Moley JF and Brunt LM: Needle biopsy of incidentally discovered adrenal masses is rarely informative and potentially hazardous. *Surgery* 142: 497-502, 2007.
- 13 Briassoulis E, Pavlidis N and Felip E: Cancers of unknown primary site: ESMO clinical recommendation for diagnosis, treatment and follow-up. *Ann Oncol* 19(Suppl 2): ii106-ii107, 2008.
- 14 Fletcher JW, Djulbegovic B, Soares HP, Siegel BA, Lowe VJ, Lyman GH, Coleman RE, Wahl R, Paschold JC, Avril N, Einhorn LH, Suh WW, Samson D, Delbeke D, Gorman M and Shields AF: Recommendations on the use of ¹⁸F-FDG PET in oncology. *J Nucl Med* 49: 480-508, 2008.
- 15 Freudentberg LS, Rosenbaum-Krumme SJ, Bockisch A, Eberhardt W and Frilling A: Cancer of unknown primary. *Recent Results Cancer Res* 170: 193-202, 2008.

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