CASE REPORT

Primary bone metastasis as first manifestation of an unknown primary tumour

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SUMMARY

Unknown primary tumour refers to a group of cancers for which the anatomical site of origin remains occult after detailed investigations. Thanks to sophisticated imaging, immunohistochemical testing and molecular-profiling tools, there is a more accurate approach to unknown primary cancer. Metastasis to bone is not a rare phenomenon, because any tumour can metastasise to bone, so it is a common clinical scenario. The role of clinical history, physical examination, laboratory tests, radiographic studies and immunohistochemistry is critical for a successful diagnostic strategy. Subsets of unknown primary cancers can be identified primarily on the basis of histopathological findings, the pattern of spread and serum markers. New immunohistochemical markers and tissue-of-origin profiles may establish presumable primary sites to unknown primary cancer on the basis of immunohistochemical and molecular patterns. We present a case of a 57-year-old woman without a cancer history, who had primary bone metastasis as the first manifestation of an occult primary tumour.

BACKGROUND

Unknown primary tumour is defined by the presence of a metastatic carcinoma without a known site of origin. It is one of a heterogeneous group of solid tumours for which the anatomical site of origin remains occult after detailed investigations. Its features include aggressiveness, early dissemination and silent primary tumour. Its clinical course is usually determined by symptoms and signs related to metastasis.¹ The most common sites for metastasis are the lungs, liver and skeleton. The incidence of metastasis as the initial manifestation of cancer is 3–4%. It is reported that 10–23% of these patients present with bone metastasis from unknown primary tumours at the time of presentation.² The primary tumour is unknown at the initial presentation in 0.5–7% of these patients, and in 15–25% of such cases, the primary site cannot be identified even at necropsy.¹ From the pathologist's perspective, most of these tumours (90%) are adenocarcinomas (60%) or poorly differentiated carcinomas (30%), 5% are squamous carcinomas and 5% neuroendocrine carcinomas.³

The primary cancer site may be asymptomatic, and the most common symptom of metastasis to bone is pain, therefore the patients seek treatment for their pain.

These tumours represent a diagnostic problem and a therapeutic challenge. Although early detection of the primary tumour can optimise treatment

and therefore improve patient outcome, most patients presenting metastasis have a poor prognosis and short life expectancy.

In this report, we describe a 57-year-old woman who presented with multiple bone metastasis due to a tumour of unknown origin.

CASE PRESENTATION

A 57-year-old woman was admitted to the hospital after elevated alkaline phosphatase (ALP) (631 IU/L) was discovered during a routine blood test. The patient was referred to our institution for further examination. The ALP elevation was isolated, and the other liver enzymes were normal (including alanine transaminase, aspartate transaminase, γ -glutamyl-transpeptidase, lactate dehydrogenase and bilirubin). The patient underwent ultrasound to confirm the hepatic origin of the elevated ALP. Ultrasound was normal, hence a bone origin was suspected.

INVESTIGATIONS

In order to rule out bone diseases, several tests were performed, which included measurement of serum calcium, parathyroid hormone, 25-hydroxy vitamin D and imaging. Initial blood tests were normal, but multiple bone metastases in the pelvic

Figure 1 CT of bone sclerosis showing: spine, pelvic bones and femora.

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Figure 2 Abnormal non-haematopoietic cells strongly suggesting an infiltrating tumour.

bones, humeri, femora and ribs were detected on a plain radiography. These lesions were mixed, osteolytic and osteoblastic.

The lesions were also found on a thoracic, abdominal and pelvic CT (figure 1). Additional investigations and imaging of the breast and pelvis, as well as tumour markers CA125, carcinoembryonic antigen, CA15.3, CA19.9, α -fetoprotein and human chorionic gonadotropin, were normal, and no other remarkable data were found in further laboratory studies. Endoscopy, mammography and breast MRI were performed, but they found no abnormalities.

As full-body CT scans failed to display any additional findings to those already mentioned, and no obvious lymphadenopathy or mass lesion was identified, bone marrow examination was performed, because such bone sclerosis suggested a haematological disorder. In the bone marrow aspirates, there were clusters of abnormal, large, non-haematopoietic cells, and low haematopoietic cellularity was observed (figure 2). The abnormal non-haematopoietic cells suggested an infiltrating tumour. Moreover, the bone marrow biopsy showed infiltrating epithelial neoplasm, forming nests, strings and glandular structures. These abnormal cells had slightly eosinophilic cytoplasm and nuclear atypia, and they were positive for CK7, CK19 and AE1-AE3 stains, and negative for CK20, TTF1, Her2, oestrogen and progesterone receptors (figure 3). Fluorodeoxyglucose-positron emission tomography (FDG-PET) did not detect any malignant lesions.

TREATMENT

Multidisciplinary (internists, oncologists, haematologists and pathologists) discussion concluded that breast and digestive

Figure 3 (Left) Clusters of abnormal cellularity in the core biopsy specimen, some forming glandular structures (H&E stain, $\times 20$ magnification). (Right) The tumour cells stain strongly for cytokeratin 7 ($\times 10$).

origins were the most likely diagnosis. Laboratory studies were non-diagnostic, but could rule out the diagnostic possibility of multiple myeloma and other haematological disorders. However, the primary tumour remained unknown, and an unknown primary cancer with bone metastasis diagnosis was established. The oncologists decided that no other analysis should be performed, and thus empiric chemotherapy (combinations of broad-spectrum antineoplastic agents) should be used, since a diagnosis of the tissue of origin was not possible. Therefore, the patient underwent empiric standard treatment with oxaliplatin and gemcitabine.

Twelve months after diagnosis, the patient's condition steadily worsened and she was referred to our palliative care unit. She passed away a month later.

DISCUSSION

Unknown primary tumour management can be challenging because of the heterogeneity of this condition and its presentation. Approximately 10% of patients newly diagnosed with cancer present with symptoms secondary to metastasis, which can be diverse, ranging from lymphadenopathy to bone pain due to skeletal metastasis. In many cases, a primary site can be suspected based on the signs and symptoms, while in some patients it is difficult to define the primary site. The proportion of patients in whom the site is identified depends on the number and accuracy of investigations and tests used.⁴

Practically all malignant neoplasms can metastasise in bone, since the skeleton is a common metastatic site for several visceral carcinomas. Metastatic disease in these patients usually occurs late in the disease process, long after the primary disease has been identified. However, 3–4% of patients with metastatic carcinoma have an unknown primary site at the time of presentation.

Bone metastases are mostly multiple, while solitary bone metastases are rare. The majority of bone metastases originate from the breast, prostate, lungs and kidneys. Bone metastases are rarely asymptomatic, and they are mostly associated with severe bone pain.⁵ They are poorly marginated lesions on proximal parts of the skeleton. Most of these patients are over 40 years of age at the time of presentation. Using a simple diagnostic strategy can identify most unknown primary carcinomas.

Tumour markers are generally not considered to be diagnostic because they are non-specific and not helpful in identifying the primary tumour site, but they may be helpful in monitoring the response to treatment. PET-CT may help to determine the extent of disease and to facilitate the design of treatment.

Regarding biological determinations, the clinical and histological settings help to determine the further evaluation of patients, and should be used in concert with immunohistochemical stains. Therefore, these stains should initially be performed on all cancers. However, not all stains will be positive or negative as might be expected in tumour cells of patients. The clinical setting suggests those stains that may be useful, and immunohistochemical patterns or profiles may suggest additional clinical testing, but it is not practical to perform every possible immunohistochemical stain on every biopsy specimen.⁶ Cytokeratins are cytoplasmatic intermediate filaments specific to epithelial cells. Thus, they are the principal positive immunohistochemistry marker of carcinomas.⁷ New genomic technologies enable the generation of profiles of gene expression at the levels of messenger RNA and microRNA. Therefore, comparison of these patterns can lead to obtain gene signatures.⁷ Recently, some classes of gene regulators have been identified. It is known that gene regulators are misregulated in cancer, and,

interestingly, they are differently expressed across different tumour types, so each tissue of origin has a unique microRNA signature.³

Patients with metastatic disease at the time of diagnosis have a poor prognosis,⁸ with an average of 11 months survival. We wish to emphasise the importance of clinicoradiological and pathological correlation in reaching a final diagnosis, especially the contribution of immunohistochemistry, which has improved the diagnosis of the unknown primary tumour, or tissue of origin. However, there is no uniform approach to performing the stains, so we must assume limitations of immunohistochemical testing, that is, factors involving the tissue heterogeneity or interobserver interpretation. What can be ruled out is probably more important than what can be confirmed. So, the immunohistochemical profile has to be interpreted with clinicoradiological findings. In the future, gene expression-based profiling, performed on biopsy material, may provide additional information to identify tumours or to guide specific anticancer therapy.^{4 7}

Finally, a word must be said about the decalcification step required for bone histomorphology. Not all fixation and decalcification procedures are suitable for samples of bone marrow, since preservation of tissue architecture and cell-specific markers can be decisive. These procedures must give good morphological detail, but should not ruin the antigenicity of the tissue. Hence, a major concern for the pathologist should be the fixation, decalcification and sectioning procedures of bone marrow

specimens. New, improved methods have been developed in order to avoid artefacts than can destroy the morphology or the immunohistochemical pattern of the sample.⁹

Customised therapy for the specific type of cancer is much more important now than a decade ago. Therefore, recognition of the tissue of origin in unknown primary cancer is also more important. The best results are seen with the combination of platinum and taxanes, which is the most widely used and recommended regimen, with response rates of about 30% and average survival of 8–11 months in selected patients. Regarding the use of non-platinum-based chemotherapy, there are several meta-analyses showing no significant benefit for any treatment group over the other in terms of survival.³ Improved diagnosis allows the use of site-specific treatment based on accurate identification of the tissue of origin, rather than empiric-based chemotherapy.

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Learning points

- ▶ Elevated serum alkaline phosphatase with a normal γ -glutamyl-transpeptidase should prompt evaluation for bone diseases.
- ▶ The most likely visceral primary carcinomas to spread to the bone include those from the lungs, kidneys, prostate, breast and thyroid.
- ▶ These tumours represent a diagnostic problem and a therapeutic challenge. Although an early detection of the primary tumour can optimise treatment and therefore improve patient outcome, most patients presenting with metastasis have a poor prognosis and short life expectancy.
- ▶ Fluorodeoxyglucose-positron emission tomography/CT should be performed early in the work-up of these patients, since its sensitivity (88–100%) and specificity (67–95%) might optimise patient management.

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