Solitary bone metastases of unknown origin

Nesrin UGRAS, Ulviye YALCINKAYA, Burak AKESEN, Ozkan KANAT

From Uludag University School of Medicine, Gorukle, Bursa, Turkey

INTRODUCTION

Practically all malignant neoplasms can metastasize to bone, even basal cell carcinomas and paragangliomas. Bone metastases are mostly multiple. Solitary bone metastases are rare, and they can be mistaken for primary tumors. The majority of bone metastases originates from breast, prostate, lung and kidney (3). The lung would be the most frequent primary site (19), but also the breast and the prostate have been mentioned as such (25). These statements should not be confused with the individual tendency of each tumor to metastasize: Berrettoni and Carter (3) deduced from an extensive autopsy study that this tendency was 84% for prostate cancer, 84% for breast cancer, 50% for thyroid cancer, 44% for lung cancer, and 37% for renal cancer.

MATERIALS AND METHODS

One hundred and twenty new cases with metastatic bone disease were referred to the authors’ pathology department between June 2005 and December 2012 ; 33 (27.5%) of these were solitary bone metastases of unknown origin, without visceral metastases. They were studied retrospectively.

No benefits or funds were received in support of this study.
There were 26 males (79%) and 7 females (21%). Their mean age was 64 years (range, 33-86 years). Only one patient (3%) was younger than 40 and only 3 patients (9%) were older than 80. The majority (51.1%) was in the age group 60-80.

Most patients presented with nonspecific symptoms, such as pain or weakness. Fractures were not noted. The biochemistry led only to non-specific data. The first hint came from chest or skeletal roentgenograms, computed tomography scans, or magnetic resonance imaging (MRI), based on the clinical data such as pain or spinal compression syndromes.

Needle biopsy or closed biopsy was performed. Immunohistochemistry was used according to the pathological features. This included, for instance, when an adenocarcinoma was suspected: cytokeratin 7 (CK7), cytokeratin 20 (CK20), thyroid transcription factor 1 (TTF1), CD10, CDX2, prostate-specific antigen (PSA), and “gross cystic disease fluid protein-15” as a marker for breast cancer (GCDFP 15).

**RESULTS**

Most metastases were found in the spine (14/33 or 42.4%), or in the pelvis (7/33 or 21.2%).

The primary site was the lung in 15 patients or 45.4%, the kidney in 6 patients or 18%, the stomach in 5 patients or 15.7%, the breast in 2 patients or 6%, the urinary bladder in 2 patients or 6%, the colorectum in one patient or 3%.

**Lung as primary site.** The overwhelming majority, namely 13 out of 15 lung patients (86.7%) had an adenocarcinoma; 2 patients (13.3%) had a squamous cell carcinoma. All 13 patients with adenocarcinoma were males, and the spine was most frequently affected: in 7 or 53.8%. The tumor cells were immunoreactive for TTF1 (Fig. 1) and CK7. Both patients with squamous cell carcinoma were females; the pelvis and the femur were affected, respectively. The tumor cells were immunoreactive for CK5/6.

**Kidney as primary site.** A clear cell carcinoma was responsible in all 6 cases: 4 males and 2 females. The metastases were located in 3 areas: 4 (66.6%) in the lower extremities (pelvis, femur, tibia), one (16.7%) in the humerus, and one (16.7%) in the spine. The tumor cells were positive for CD10 (Fig. 2).

**Stomach as primary site.** All 5 patients, 4 males and one female, had a signet-ring cell adenocarcinoma. Were affected: the spine in 3 (60%), the pelvis in one (20%), and a rib in one (20%) patient. The tumor cells showed a strong positive reaction for CK7; not for CK20 and CDX2 (Fig. 3).

**Breast as primary site.** Both patients had an invasive ductal carcinoma, which had metastasized to the spine and to the femur, respectively. The tumor cells reacted to GCDFP15, and the estrogen receptors were positive; CK7, CK20 and CA125 had no effect.

**Prostate as primary site.** An adenocarcinoma was diagnosed in both cases: Gleason score 5 + 4. The humerus and the pelvis were affected. The tumor cells were positive for CK7, CK20, high molecular weight cytokeratin, and PSA.

---

**Fig. 1.** – Photomicrograph of bone metastasis from lung adenocarcinoma. A: Glandular formation of neoplastic cells (H&E, × 50). B: Tumor cells positive for TTF-1 (× 100).

**Fig. 2.** – Photomicrograph of bone metastasis from clear cell carcinoma. A: nests of cells with vesicular chromatin and abundant clear cytoplasm (H&E, × 50). B: strong CD10 staining (× 100). C: strong Vimentin staining (× 100).
Urinary bladder as primary site. Both male patients had an urothelial carcinoma. Solitary metastasis to rib and tibia, respectively.

Colorectum. A single male had an adenocarcinoma with typical signet-ring cells. It metastasized to the spine. The tumor cells were positive for CK20 and CDX2, and negative for CK7, PSA, and high molecular weight cytokeratin (Fig. 4).

The survival period from the time of diagnosis until death or to the last control was available in 21 of the 33 patients. The median survival period was 8.7 months (range, 2-23). The survival rate dropped rapidly, with only 23.8% of patients alive at 6 months and only 9.5% alive at 12 months. Adenocarcinoma of the lung had the worst prognosis.

DISCUSSION

This retrospective study was restricted to patients who had a solitary bone metastasis as the only manifestation of an undetected primary tumor. They constituted 27.5% of a group of 120 patients with bone metastases of unknown origin. Most solitary bone neoplasms are secondary or metastatic rather than primary: the ratio is 17/1 to 25/1 (18). Bone metastases are rarely silent: they are mostly associated with severe bone pain. Most cancer patients do not die from the primary tumor, but rather from their visceral metastases. There is controversy about the most frequent occult primary cancer: lung, breast and prostate have been mentioned (19,25). Of course, also the type of tumor plays a role: Nystrom et al (24) found a completely different spectrum in 266 patients with metastatic non-squamous carcinoma of unknown origin: the most frequent primary site was the pancreas (20%).

Lung as the primary site. Jaukovic et al (12) found that 57 (57%) of their 100 patients with lung cancer had a positive bone scintigram, which stresses the tendency of lung cancer to metastasize to the skeleton; only 6 of these 57 patients had a solitary metastasis. Tsuya et al (30) reported a rate of 30.4% skeletal metastases in 259 patients with non-small cell lung cancer.

Kidney as the primary site. Shvarts et al (27) noted bone metastases in 14% of their 1357 patients with renal cell carcinoma; a “T1-T4 ECOG greater than 0 disease” was an important predictor of bone metastases. According to Brinkmann et al (6) the average survival of renal cell carcinoma patients was 24 months, after immunochemotherapy and radiation. Hoffmann et al (9) reported that clear cell renal cell carcinoma is more likely to metastasize to the lungs, while chromophobe renal cell carcinoma is more likely to metastasize to the liver.

Stomach as the primary site. Bone metastases from gastric cancer are uncommon (1), with an inci-
dence of only 13.4% in autopsy specimens (21). The mechanism of bone metastasis in gastric carcinoma has been investigated by several authors. Lehnert et al (17) suggested that the high percentage of bloodborne metastases in recurrent early gastric cancer may be related to the rich vascularity of the gastric mucosa. Batson (2) felt that metastasis to the spine from the stomach may occur through the paravertebral venous plexus because the intraabdominal pressure is raised. Several studies have demonstrated the prognostic significance of histopathologic subtypes (for instance signet-ring cell carcinoma) in gastric carcinomas (20,29). Kobayashi et al (15), for instance, reported that the depressed-type signet-ring cell carcinoma constitutes a risk factor for bone metastasis from early gastric cancer. In the current study all 5 cases had signet-ring cell carcinoma of the stomach.

Breast as the primary site. Worldwide, breast cancer is the most common type of cancer in women. Bone is the commonest site to which breast cancer metastasizes (8). The skeleton is also the most common site of first distant relapse in breast cancer (4). The mechanisms responsible for tumor growth in bone are complex and involve tumor stimulation of the osteoclasts and the osteoblasts, as well as the response of the bone microenvironment (7). Borst et al (5) reported that the metastatic patterns of lobular and ductal carcinoma of the breast are different: in lobular carcinoma metastases to the gastrointestinal system, the gynecologic organs and the peritoneum-retroperitoneum are markedly more prevalent. In their series of 2605 breast tumors, lobular carcinoma accounted for 14% and ductal carcinoma for 86%. Also in the current study both solitary breast metastases were of the more common ductal subtype.

Prostate as the primary site. Prostate cancer has a great tendency to metastasize to the skeleton: an 84% chance according to an autopsy study by Berrettoni and Carter (3). Bone metastasis is a hallmark of advanced prostate cancer. The tumour spreads via the venous plexus, especially to the pelvis and to the lumbar spine.

Urinary bladder as the primary site. Urinary bladder cancer is the second most frequent cancer of the genitourinary tract, after kidney cancer. Urothelial carcinoma of the bladder is the commonest histologic type; it metastasizes to lymph nodes, liver, lung, bone, and adrenal gland (16). Taher et al (28) reported that in muscle-invasive bladder cancer the cumulative 3-year incidence of bone metastases in the non-metastatic patients after treatment mounted to 19.4 +/- 4.4%. The authors found that the urinary bladder accounted for 6% of the solitary bone metastases, exactly like the breast and the prostate.

Colorectum as the primary site. Cancer of the colorectum is one of the most frequently diagnosed malignancies in both men and women. Colon adenocarcinomas often metastasize to regional lymph nodes and then hematogenously to liver and lungs, late in the course of the disease (26). Katoh et al (14) detected bone metastases from colorectal cancer in 28 out of 118 autopsies (23.7%) in patients with primary colorectal cancer, treated either surgically or conservatively. Kanthan et al (13) reported that solitary skeletal metastases from a primary colon carcinoma are rare, with an incidence of 1.1%. As to the various subtypes of colorectal cancer (mucinous, ring-cell, adenocarcinoma): the signet-ring cell subtype has a worse outcome (23).

Flowchart for the clinician

History and physical examination, biochemistry with tumor markers and immunoelectrophoresis, chest radiograph, CT-scan of chest and abdomen, and bone scan constitute an ideal algorithm, according to Katagiri (19).

Weakness

The authors did not use bone scintigraphy. This would probably have revealed more bone metastases, so that certain metastases could no longer be considered as solitary.

REFERENCES
