

Case Report

Searching for the Culprit: Metastases from a Cancer of Unknown Primary

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Keywords

Cancer of unknown primary · Metastasis · Breast cancer

Abstract

We report a case of metastases from a cancer of unknown primary whose primary site could not be identified during the appropriate pretreatment evaluation. The patient was a 58-year-old woman with a history of passive smoking and with no history of cancer in the family. Her current condition started with asthenia, adynamia, and pallor, followed by palpitations. An abdominopelvic computed tomography (CT) scan was performed, showing multiple osteolytic lesions distributed in all bone structures and axillary adenopathy on the left side. As part of the approach and given the high suspicion of multiple myeloma, tests were performed. The results were negative for multiple myeloma. A PET-CT scan was performed and showed left axillary adenopathy. The breasts and other organs were not affected. Left axillary lymph node resection revealed breast primary metastatic pleomorphic lobular carcinoma. Due to the metastatic disease (caused by the primary breast cancer), it was decided to start chemotherapy.

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Background

Cancer of unknown primary (CUP), also called “occult primary cancer,” is defined as a set of malignant metastatic tumors confirmed by pathology, whose primary site cannot be identified during the appropriate pretreatment evaluation. CUP includes a metastatic cancer confirmed by the following: complete clinical history, physical examination, laboratory studies, imaging, and invasive procedures according to the presentation along with a pathological evaluation with hematoxylin and eosin stains and immunohistochemistry. The clinical presentation of this group of malignancies is diverse and they are characterized by having a poor prognosis, with a median survival rate of 6–9 months [1]. The primary site of the CUP is identified in less than 30% of the occasions and even in autopsies it can only be successfully identified in 20–50% of the cases. In the United States in 2011, there were 31,000 new cases of CUP, which accounted for 2% of all cancers in the same country. Both genders are affected equally, with a median age at presentation of 60 years. Unfortunately, there is a lack of specificity in the registry in terms of identifying the cause of death by CUP [2].

Case Presentation

We report the case of a 58-year-old woman with a history of passive smoking for 20 years, with no history of cancer in the family, a personal history of major depressive disorder treated with desvenlafaxine 37.5 mg/day since 2012, and hypercholesterolemia treated with rosuvastatin 10 mg/day since 2013. She had a surgical history of hemorrhoidectomy, hysterectomy due to uterine myomatosis, and cesarean section. Her current condition started in January 2015 with asthenia, adynamia, and pallor. In February of the same year, palpitations were added. She denied dyspnea or an anginal equivalent. She was referred to a hematologist who performed a blood count where microcytic hypochromic anemia was documented (Hb 6 g/dL) compatible with iron deficiency, and intravenous iron treatment was started. Panendoscopy revealed grade B esophagitis, nodular gastropathy in the antrum and body, and bulb duodenitis with minimal bleeding. Colonoscopy was reported as normal. Gastric, duodenal and ileal biopsies were negative for malignancy. Complementary blood tests revealed high alkaline phosphatase levels of 154 U/mL, so an abdominopelvic computed tomography (CT) scan was performed, finding multiple osteolytic and osteoblastic lesions distributed in all bone structures, unspecified lesions in both ovaries, hepatic cysts, bilateral urinary tract dilation and a 14-mm axillary adenopathy on the left side. Hospitalization was the next course of action.

Discussion

As part of the approach and given the high suspicion of multiple myeloma, the following tests were performed: bone marrow aspiration and biopsy, protein electrophoresis in serum and 24-h urine, and total serum immunoglobulins. The results were negative for multiple myeloma, and bone marrow biopsy showed poorly differentiated metastatic adenocarcinoma with ring cells (Fig. 1). The most common malignant bone tumor is metastatic carcinoma, the most common primary bone tumor is multiple myeloma, and the most common primary solid

bone tumor in adults is osteosarcoma [3]. It is hypothesized that the reason for the cancer to be a CUP is due to the fact that there was regression of the primary tumor after the metastases or that the primary is too small to be detected with the current imaging techniques. Other authors suggest that the primary tumor can no longer be elucidated since it was eliminated or contained by the immune system. Sometimes, years after the treatment of metastatic disease, the phenomenon of “appearance of the primary tumor” may occur and be evident even if the initial lesions of the CUP have disappeared [4]. The patterns of presentation may suggest a CUP, although it should be taken into account that these tumors can metastasize to any location. Therefore, the approach is quite complicated and should not be limited to the form of presentation. By light microscopy, 5 subtypes of CUP can be identified: moderate adenocarcinoma (well differentiated) (60%), undifferentiated adenocarcinoma (29%), squamous cell carcinoma (5%), undifferentiated carcinoma (3%), and neuroendocrine carcinoma (2%) [5]. Immunohistochemistry helps in the approach of CUPs when they are poorly differentiated or undifferentiated tumors. These techniques are not specific or completely sensitive; they have not improved outcomes and should be guided by the available clinical information to avoid a broad panel of tests [6]. To support the immunohistochemical study in carcinomas, cytokeratins 7 and 20 can be used (Table 1); however, the expression of antibodies can change with the development of metastases [7, 8]. Therefore, a series of “organ-specific” markers should be completed to make a more precise diagnosis (Table 2) [9–11]. Due to the presence of the axillary ganglion, a digital mammography and bilateral ultrasound were performed, and the results were negative for malignancy. Pelvic ultrasound showed no alterations in both ovaries. PET-CT manages to identify between 27 and 57% of the CUPs and the reported sensitivity is around 84%. More prospective studies are needed in order to compare this modality versus traditional imaging studies, and to be able to measure the impact on the overall survival of patients [12]. The PET-CT scan showed lytic lesions with hypercaptation at the spine, pelvis, femur, right humerus, parietal and frontal bone, left axillary adenopathy, and left ovary. Breasts and other organs were not affected (Fig. 2). Left axillary lymph node resection revealed breast primary metastatic pleomorphic lobular carcinoma in 1 of 2 axillary lymph nodes. Estrogen receptors were positive in 90% of neoplastic cells, progesterone receptors were positive in 1%, HER2 receptors were negative and Ki67 receptors were positive in 30% (Fig. 3). Due to the metastatic disease (caused by the primary breast cancer), it was decided to start palliative chemotherapy with paclitaxel 80 mg/m² weekly for 12 weeks. The prognosis of patients with CUP is divided into two main groups, favorable and unfavorable. The first one includes: female gender and limited and potentially resectable metastatic disease. However, most of the patients belong to the unfavorable prognosis group: male gender, adenocarcinoma with metastasis to various organs, and central nervous system disease [13]. The chemotherapy that has mostly been used in patients with CUP is based on platinum and taxanes, specifically carboplatin plus paclitaxel. This scheme is the most experienced worldwide, and the number of cycles is determined by the tolerance and response to the treatment in each patient [14]. There are currently three commercial research studies of microarrays of 1,500 genes created from databases of 15 tumor tissues and 60 histological morphologies. The molecular study establishes a “result of similarity” on a scale of 0–100% for each of the 15 tumors. With a result of ≥30% it is “tissue of probable origin,” 5–29% is “undetermined,” and <5% is “not similar.” In 2008, the FDA approved its use for the study of unknown primary tumors [15]. The international guidelines recommend that until more evidence exists, the routine use of

molecular profiles should be restricted only to those patients in whom the pathological evaluation inclines only towards the carcinoma spectrum. This new technology is promising; it only requires small tissue samples and immunohistochemistry to complement it. The impact on global survival is currently unknown given the difficulty of diagnosis, which requires highly specialized equipment and personnel, as well as 2 weeks for a final report. There are no direct comparisons between each of the available kits [2].

Conclusion

CUP is one of the main problems in medical oncology due to its complex diagnosis and therefore the delay of treatment. The presentation patterns of the CUP are of great importance because they can suggest the location of the same, although due to its metastatic spread to any location, the approach is quite complicated. As of today, diagnostic techniques are not very specific and sensitive, so the diagnosis must be guided by the clinical features to avoid the use of unnecessary tests. The prognosis of patients with CUP relies on multiple factors; therefore, early diagnosis and initiation of therapy is of vital importance.

Statement of Ethics

Informed consent was gained from the patient for publication of this case report and the accompanying images.

Disclosure Statement

The authors deny any conflict of interest.

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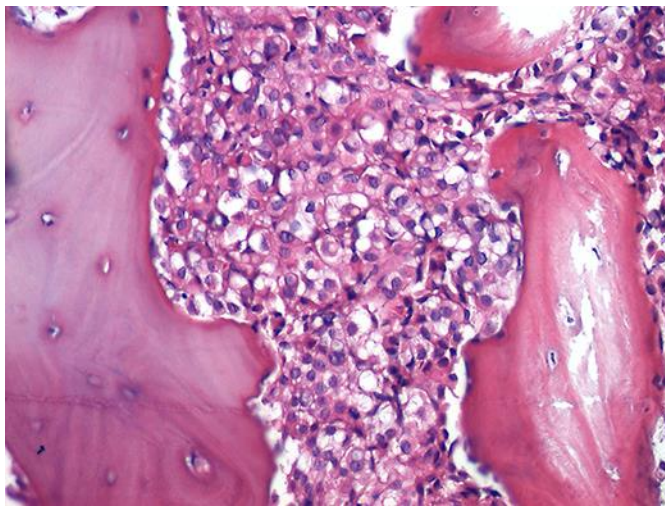


Fig. 1. Bone marrow biopsy (hematoxylin and eosin stain) that shows bone trabeculae and medullary space with diffuse infiltration by a malignant epithelial neoplasm with a pattern of solid growth constituted by large cells, with an inconspicuous nucleolus and a vacuolated cytoplasm. Some of the cells have the nucleus rejected to the periphery. It was interpreted as a poorly differentiated adenocarcinoma. $\times 40$ (from Rita Dorantes-Heredia).

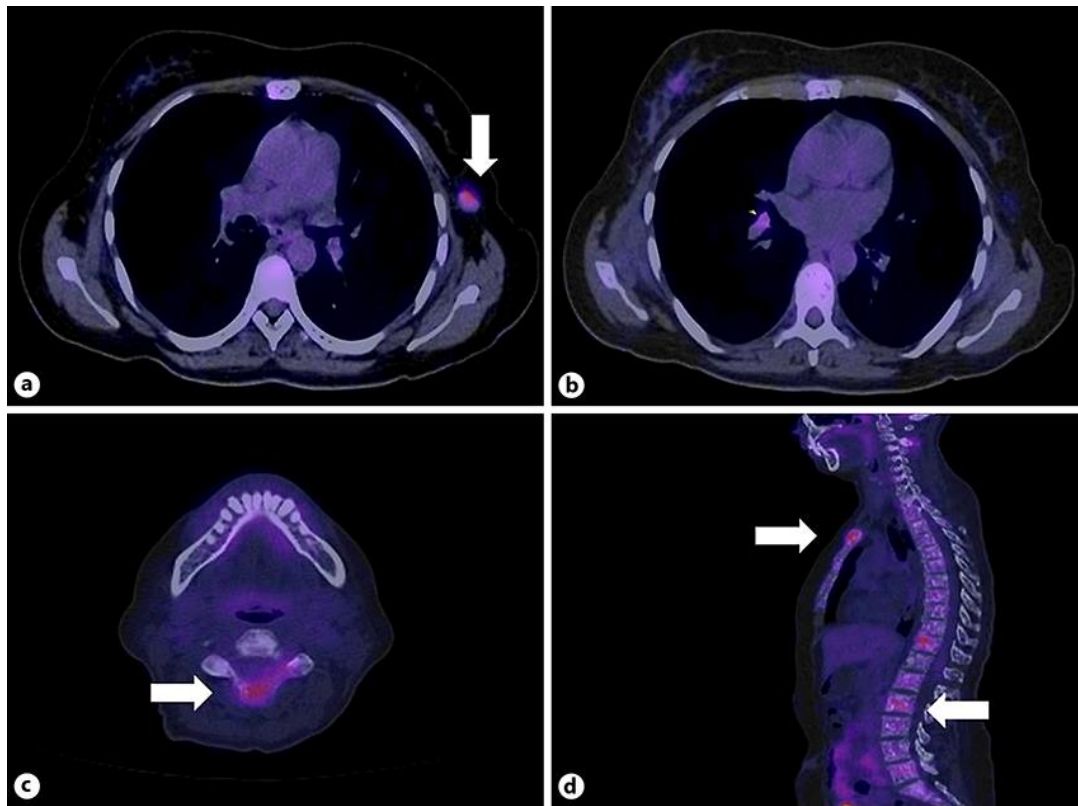


Fig. 2. PET-CT with 18-fluorodeoxyglucose. **a** Axial thoracic section that shows hyperuptake in the left axillary ganglion without other hyperuptake sites. **b** There was no uptake at the level of breast glands or other sites at this section. **c** Osteoblastic lesions were found at the cervical level number 4. **d** Hypercaptation appreciated in osteolytic and blastic lesions in vertebral bodies at various levels of the dorsal and lumbar spine and sternum.

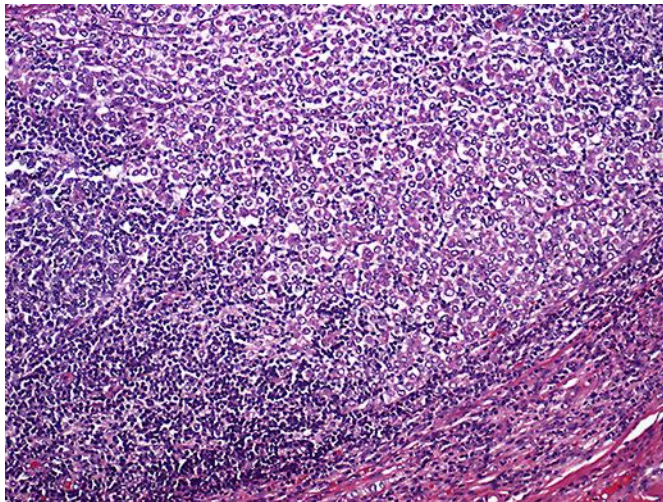


Fig. 3. Lymph node (hematoxylin and eosin stain) that shows diffuse infiltration by a poorly differentiated malignant epithelial neoplasm, with a solid growth pattern constituted by large cells with small nucleolus and moderate vacuolated eosinophilic cytoplasm. Many of the cells have the nucleus rejected to the periphery. The morphology is compatible with breast primary pleomorphic lobular carcinoma. $\times 40$ (from Rita Dorantes-Heredia).

Table 1. Immunoprofile of cytokeratins (CK) 7 and 20 in neoplasms

CK7+/CK20+	Urothelial carcinoma Pancreatic carcinoma Mucinous ovarian carcinoma
CK7+/CK20-	Non-small cell lung cancer and small cell lung cancer Breast carcinoma Non-mucinous ovarian cancer Endometrial adenocarcinoma Mesothelioma Epidermoid carcinoma of the cervix
CK7-/CK20+	Colorectal adenocarcinoma Merkel cell carcinoma
CK7-/CK20-	Pulmonary epidermoid carcinoma Prostate adenocarcinoma Renal cell carcinoma Hepatocellular carcinoma Adrenal carcinoma Thymic carcinoma

Table 2. Antibodies used in organ-specific immunohistochemistry

Antibody	Commonly used to identify	Can also be expressed in
TTF-1	Pulmonary adenocarcinoma	Thyroid carcinoma
CDX2	Carcinoma of gastrointestinal tract	Carcinomas of the pancreato-biliary tract Bladder carcinomas Carcinomas of the intestinal type of ovary or lung
RE/RP	Breast carcinoma Endometrial carcinoma	Ovarian and lung carcinomas Neuroendocrine tumors
CA-125	Ovarian tumors	Mesothelioma Pancreatic, hepatic, and biliary carcinomas Bladder adenocarcinoma Endocervical adenocarcinoma
PSA	Prostate tumors	Salivary gland tumors Breast tumors
Hep par-1	Hepatocellular carcinoma	Gastric carcinoma
Thyroglobulin	Follicular thyroid carcinoma	–
RCC	Renal clear cell carcinoma Papillary renal cell carcinoma	Yolk sac tumor Embryonal carcinoma Mesothelioma
ACE	Lung, colon, stomach, bladder, endocervix, breast carcinomas, and chordomas	–
EMA	Synovial sarcoma Synovial epithelium sarcoma Meningioma Choroid plexus carcinoma Chordoma Ependymoma	–
WT1	Wilms tumor	Mesothelioma Serous ovarian carcinoma Desmoplastic small round cell tumor
HMB45	Melanoma	Smooth muscle tumor Perivascular epithelioid cell tumor Clear cell sarcoma Low-grade endometrial stromal sarcoma
Melan-A	Melanoma	Adrenal tumor Perivascular epithelioid cell tumor Clear cell sarcoma
Chromogranin, synaptophysin, CD56	Neuroendocrine tumors	Ewing's sarcoma/primitive neuroectodermal tumor Paragangliomas Medullary thyroid carcinoma