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Solitary Soft-Tissue Metastasis of a Pancreatic Adenocarcinoma 2 Years After Curative Resection: Report of a Rare Case and a Literature Review

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 74-year-old
Final Diagnosis: Soft tissue metastasis from pancreatic adenocarcinoma
Symptoms: Palpable, hard and painful mass, with rapid growth, located in the posterior aspect of the upper left thigh
Medication: —
Clinical Procedure: —
Specialty: Surgery

Objective: Rare disease

Background: Soft-tissue metastases from a primary carcinoma are rare lesions. They often are the first clinical manifestation of a previously unknown malignancy of an advanced stage, but may also be solitary in a setting of a recurrent disease. Generally, they are associated with poor prognosis and may be the source of diagnostic confusion both clinically and pathologically. The primary location of the malignancy is usually lung, breast, kidney, or colon. Soft-tissue metastases from a pancreatic adenocarcinoma are extremely rare. A few cases involving the skin have been described in the literature, and solitary metastasis to the deep soft-tissue (eg, subcutis and skeletal muscle) was reported less than 10 times.

Case Report: We report the case of a 74-year-old woman who presented with late-onset (recurrent disease), solitary, subcutaneous metastasis in the posterior aspect of the left thigh, deriving from a pancreatic head adenocarcinoma, 2 years after initial treatment with R0 resection (pancreaticoduodenectomy) and adjuvant chemotherapy. We emphasize the rarity of this entity, review the literature, and discuss treatment options.

Conclusions: Solitary soft-tissue metastasis from a pancreatic adenocarcinoma after initial curative treatment is very rare. Although hematogenous spread from a pancreatic adenocarcinoma generally has a very poor prognosis, treatment should be individualized according to the patient's history, general condition, and symptoms and the clinical setting in relation to the primary disease.

Keywords: Carcinoma, Pancreatic Ductal • Neoplasm Metastasis • Neoplasms, Connective and Soft Tissue

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Background

Pancreatic adenocarcinoma is an aggressive malignancy with poor prognosis. The most common sites of metastases are the regional lymph nodes, the peritoneum, the liver, and the lungs [1]. Distant soft-tissue metastases, on the contrary, are rare and occur most often in the skin, with subcutaneous and skeletal muscle localization being the absolute exception. We report a very rare case of a woman with a solitary, subcutaneous metastasis of an adenocarcinoma of the pancreas head that presented as a painful mass in the left thigh 2 years after pancreaticoduodenectomy and adjuvant chemotherapy. To the best of our knowledge, except from the present report, only 6 cases of subcutaneous or skeletal muscle distant metastasis from pancreatic adenocarcinoma has been described in the literature [2-7].

Case Report

A 74-year-old woman presented in our department with painless obstructive jaundice during the last 2 weeks. The patient's medical history included arterial hypertension and hyperthyroidism under medical treatment, as well as surgical history laparoscopic cholecystectomy 10 years ago. The clinical, laboratory, and imaging evaluation (CT, endoscopic US-guided biopsies, and ERCP) of the patient revealed an adenocarcinoma of the pancreatic head with no evidence of distant metastases. The patient underwent a pylorus-preserving pancreaticoduodenectomy (Longmire-Traverso) with lymphadenectomy. The postoperative course was uneventful and the patient was discharged on the tenth postoperative day. Histopathological analysis of the specimen showed a poorly differentiated, 4.9-cm diameter, pancreatic ductal adenocarcinoma that extended to the duodenum. The surgical margins were free and metastasis was found in 2 of the 14 resected lymph nodes (T3, N1, M0). The patient received adjuvant chemotherapy (gemcitabine i.v. 6 cycles+capecitabine p.o.) and the follow-up period was uneventful until 2 years after primary diagnosis, when she first noticed a deep, palpable, hard, and painful mass, with rapid growth, located in the posterior aspect of the upper left thigh. The clinical characteristics of the tumor were highly suspicious for malignancy, therefore magnetic resonance imaging (MRI) was conducted as initial imaging, which revealed a round mass approximately 4 cm in diameter, located in the deep subcutaneous tissue of the posterior aspect of the left thigh, with low signal on T1-weighted sequences (**Figure 1**) and high signal on T2-weighted sequences (**Figure 2**). After injection of gadolinium-diethylenetriamine penta-acetic acid (Gd-DTPA), the tumor showed strong peripheral enhancement with central hypoattenuation and peritumoral edema and was suspicious of malignancy (**Figure 3**). A total-body CT scan was performed, which excluded recurrent disease in other sites and the decision was taken to resect the tumor (**Figure 4**). The histopathological analysis of the specimen revealed a round tumor 4 cm in diameter with areas of cystic degeneration and hemorrhagic necrosis and diffuse peritumoral chronic inflammatory infiltration, with cell characters of an adenocarcinoma (**Figures 5, 6**) The surgical margins were free (R0 resection) (**Figure 7**). Immunohistochemical analysis was not performed due to the medical history (known adenocarcinoma of the pancreas).

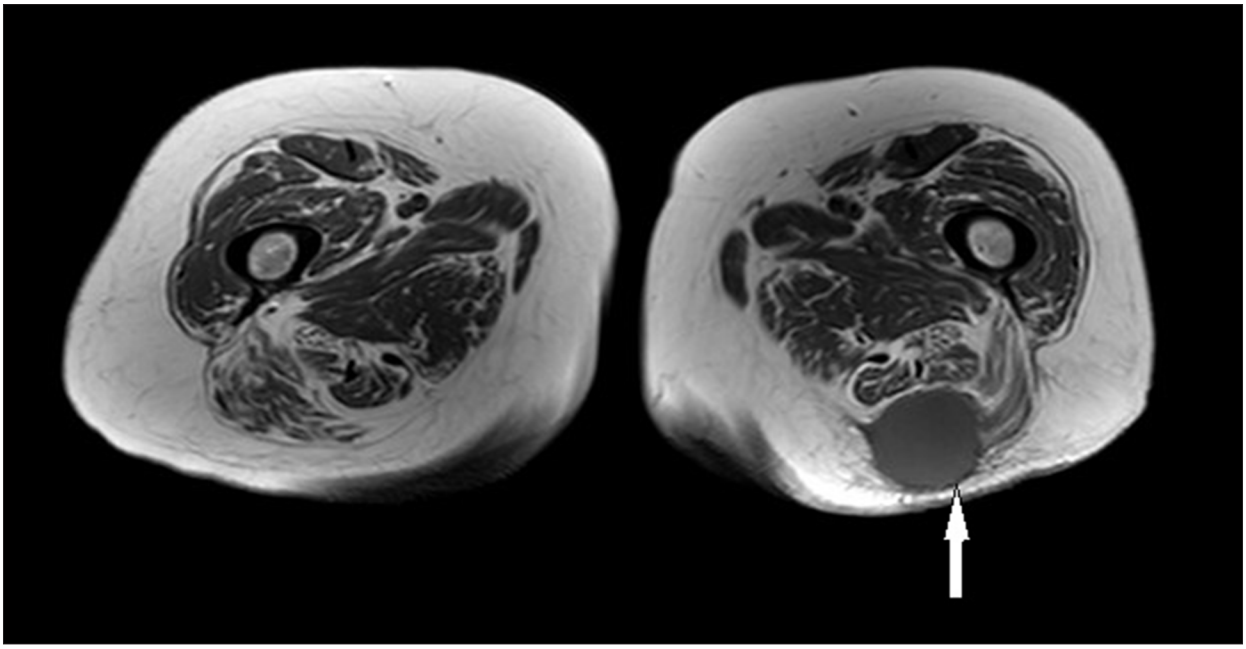

Figure 1. Axial T1-weighted MRI sequence depicting a homogenous low signal intensity tumor (white arrow).

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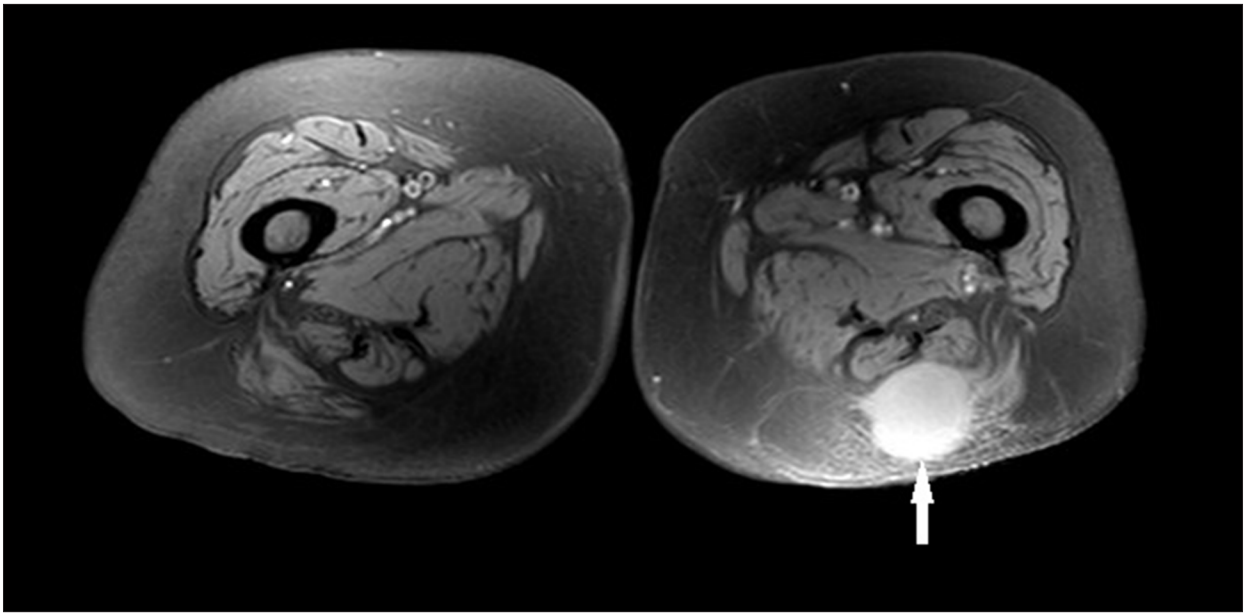

Figure 2. Axial T2-weighted MRI sequence depicting a homogenous high signal intensity tumor (white arrow).

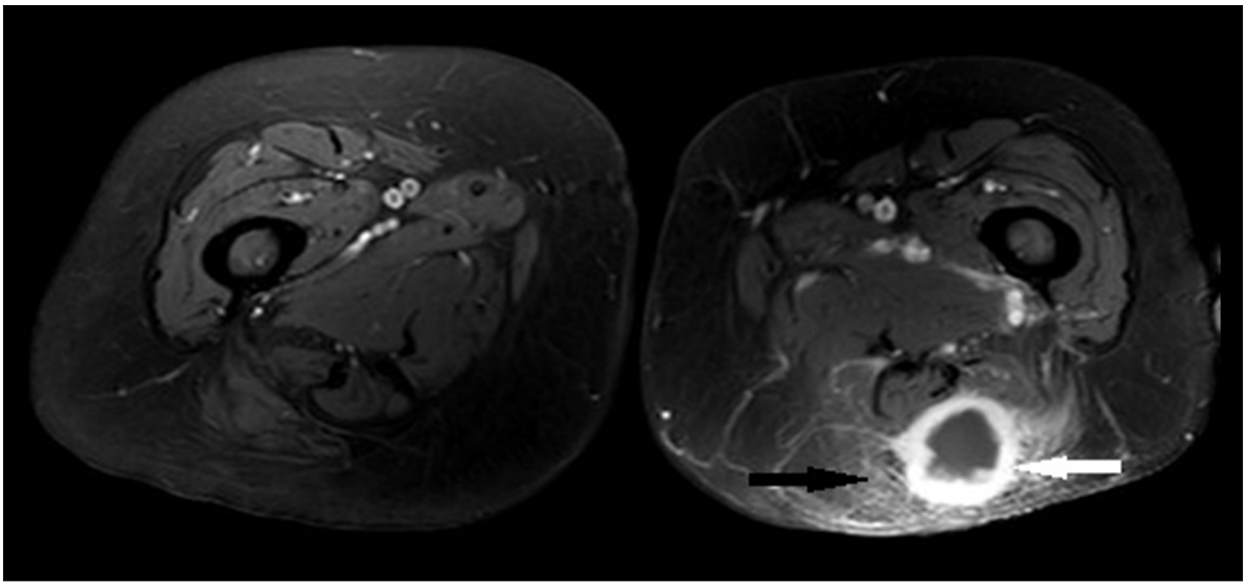

Figure 3. After injection of Gd-DTPA, the tumor shows strong peripheral enhancement (white arrow) with central hypoattenuation and peritumoral edema (black arrow).

The postoperative course was uneventful. Afterwards, she again received adjuvant chemotherapy (gemcitabine i.v. 3 cycles) and to date (8 months later) she remains free of disease.

Discussion

Despite the fact that soft tissue comprises about half of our total body mass, distant metastases to these areas are rare and account for about only 0.36% of all soft-tissue tumors [8]. Most cases found in the literature result from either single reports or small case series. The rarity of these metastases can be partly explained through several characteristics of soft tissue, such as variable and turbulent blood flow in comparison to other organs (eg, liver and lungs) [9], production of several anti-cancer factors (eg, leukemia inhibitory factor and interleukin 6) [10], and constant trauma to tumor cells caused by muscle contraction [11], which all lead to resistance of tumor cell embedding.

Soft-tissue metastases may involve the cutaneous, subcutaneous, or muscle tissue and can occur as a solitary tumor or as

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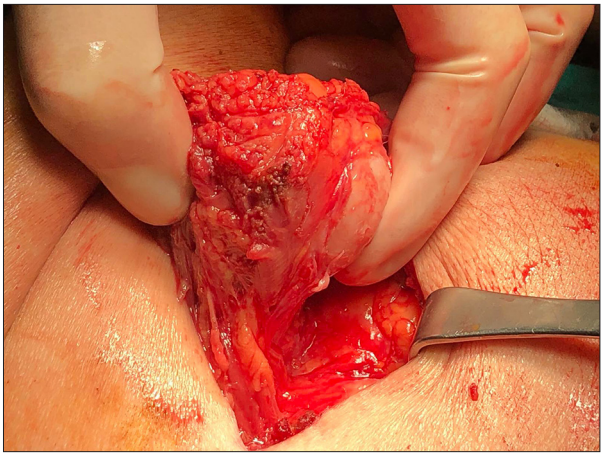

Figure 4. Intraoperative photo of the tumor located subcutaneously, after mobilization from the surrounding tissue.

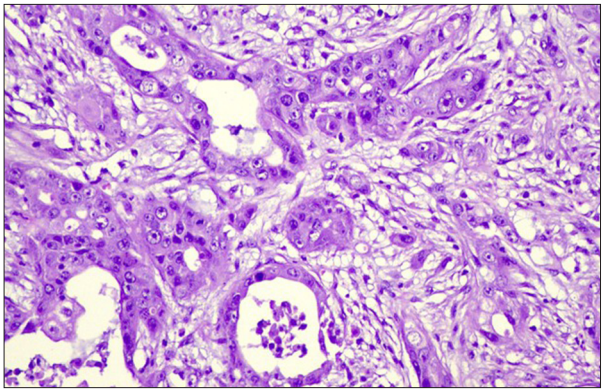

Figure 6. H&E, magnification scale ×200: At higher magnification, the carcinomatous cells consist of eosinophilic cytoplasm, with a high nuclear/cytoplasmic ratio, and atypical nuclei, in various sizes, with prominent nucleoli.

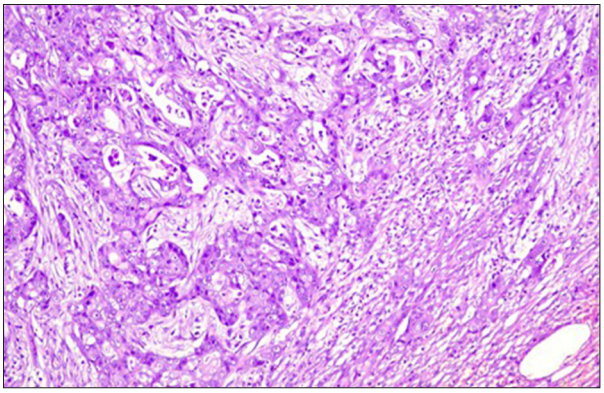

Figure 5. H&E, magnification scale ×100: Neoplastic cells forming adenoid and cribriform tumor clusters, invading surrounding connective tissue with desmoplastic reaction.

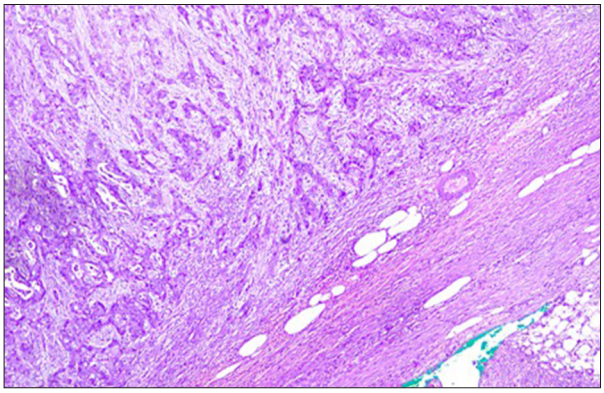

Figure 7. H&E, magnification scale ×40: High-grade adenocarcinoma infiltrating fibrous connective and fatty tissue. Green stain indicates the peripheral surgical margin.

disseminated disease. Subsequently, they may present as concurrent lesions at the time of first diagnosis, as the first clinical manifestation of an occult malignancy of unknown site, or they may present as late-onset (recurrent) disease after successful treatment of the primary malignancy, with a mean disease-free interval of 77 months, as estimated in a small case series of 16 patients with soft-tissue metastases from primary carcinomas [7]. Regardless of the above, soft-tissue metastases represent an advanced state of disease and are associated with a poor prognosis, with a mean survival of 1-19 months [12].

The most common histological type of primary malignancy that is associated with soft-tissue metastases are carcinomas arising from the lung, the kidneys, and the gastrointestinal tract, with most being adenocarcinomas, squamous cell and clear cell carcinomas, although other types have also been described in the literature [13,14].

In one of the largest series published, with a total of 121 cases [12], the most common primary carcinoma associated with distant soft-tissue metastasis was lung carcinoma (n=38) followed by renal carcinoma (n=14), colon carcinoma (n=9), and carcinoma of unknown origin (n=8), but pancreatic adenocarcinoma was involved in only 1 case [2]. Regarding the anatomical sites of the metastasis, the thighs, psoas, lumbar paraspinals, and gluteals were the most common, with 28, 13, 12, and 11 cases reported, respectively [12].

In another, more recent large series, the authors reported their 30-year experience at an academic medical center, presenting a total of 118 cases of soft-tissue metastases [13]. According to their results, 83 of the soft-tissue metastases originated from a carcinoma. In contrast to the previously mentioned case series [12], after the lungs, breast carcinomas were the second most common primaries, followed by the kidneys and colon. The soft-tissue metastasis presented as a solitary

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tumor in 70.3% of cases and as disseminated disease in 2.5%. Furthermore, in 27% it was the initial clinical manifestation of the disease, whereas in 13.5% of cases the primary site of malignancy could not be identified. Finally, the most common anatomical sites of the metastases were the abdominal wall, followed by the scapular region and thighs.

Diagnosis of soft-tissue metastases from a primary carcinoma can be challenging. Depending on the anatomical site and the tissue affected (eg, cutaneous, subcutaneous, muscular) by the tumor, differential diagnosis includes various skin pathologies, primary sarcoma, and non-neoplastic lesions such as hematoma, abscess, and myositis ossificans [15]. Regarding the clinical signs, pain, in contrast to the primary sarcomas [16], is the most common leading symptom, especially if the muscular tissue is involved. Patient history, MRI, and histopathological evaluation via core needle or excisional biopsy are the main tools used to establish the diagnosis [12]. Soft-tissue metastases often appear on MRI with low signal on T1-weighted sequences, high signal on T2-weighted sequences, strong peripheral enhancement with central necrosis, surrounding edema, and sometimes microcalcifications [12,16]. 18F fluorodeoxyglucose positron emission tomography/computed tomography (F-18 FDG PET/CT) may also be used for diagnostic purposes; its sensitivity is equal to that of MRI and is also a useful tool to exclude disseminated disease [17]. Finally, especially in cases of a previously unknown primary malignancy, immunohistochemistry may be useful to distinguish between a primary sarcoma and a metastasis and to identify the primary site of a carcinoma. Use of a basic panel that includes epithelial markers such as broad-spectrum cytokeratin, markers associated with either pulmonary (thyroid transcription factor 1 [TTF1]) or gastrointestinal differentiation (transcription factor CDX2) and markers of soft-tissue sarcomas, such as smooth muscle actin (SMA), Desmin, S-100, CD 34, and CD 117, is generally recommended [13].

Treatment of soft-tissue metastases depends upon the clinical setting in relation to the primary disease (concurrent lesion or recurrence after treatment of primary disease), upon the symptoms and general condition of the patient, and upon the histological type and extent of the metastasis (local or disseminated disease). As already mentioned, metastatic lesions from a primary carcinoma are associated with a poor prognosis and an overall mean survival time of 15.36 months, with lung carcinoma carrying the worst prognosis of 6.7 months [18]. Consequently, treatment should be palliative and includes observation, radiotherapy±chemotherapy, or excision. While excision of small lesions for diagnostic purposes (excisional biopsy) or to control excessive pain is a generally acceptable, excision with curative intent with wide margins should be used only for highly selected cases. Patients in good general condition, with a solitary soft-tissue metastasis, after initial successful treatment of primary disease and long disease-free interval and ideally with a favorable histology (for example renal cell carcinoma), are the only potential candidates for radical excision [12,16]. Indeed, a few such cases with long-term survival over 5 years have been reported in the literature [16,19,20].

Pancreatic adenocarcinoma is an aggressive malignancy and continues to have a poor prognosis, despite significant progress made in diagnostic and therapeutic procedures. At the time of diagnosis, in most cases the tumor is either locally advanced or has already metastasized to distant organs [1].

The most common sites of distant metastases for pancreatic adenocarcinoma are the peritoneum, liver, lungs, adrenal glands, kidney, bone, and brain [1]. Soft-tissue distant metastases on the contrary, are rare and usually involve the skin. Skin lesions are most commonly found in the umbilical region, as a result of direct spread of peritoneal carcinomatosis through the remnant of the obstructed umbilical vein ("Sister Joseph's nodule") [5]. On the contrary, no more than 34 cases of extra-umbilical cutaneous metastases from pancreatic adenocarcinoma have been described so far in the literature, located in several different sites such as the face, neck, scalp, chin, axilla, chest, abdomen, buttocks, scrotum, or even labia majora [21,22]. Interestingly, distant metastases from pancreatic adenocarcinoma exclusively involving the deeper layers of the soft tissue (subcutis and skeletal muscle) are even more rare. To the best of our knowledge, except of our case, only 6 more cases has been described so far in the literature – 5 in single reports [2-6] and 1 in a case series [7]. The rarity of this phenomenon may be partly explained by the resistance of the soft tissue and especially the muscular tissue to tumor cell implantation and the high malignancy potential of pancreatic adenocarcinoma. In other words, patients with pancreatic adenocarcinoma usually do not live long enough to develop a distant, deep, soft-tissue metastasis, which occurs in the late stage of disease.

0In our patient, a solitary, deep, soft-tissue metastasis, located in the posterior aspect of the left thigh was diagnosed 2 years after successful primary treatment of a pancreatic head adenocarcinoma. The patient presented in our department with a painful mass in this area, a symptom common in deep soft-tissue metastases but less common in skin metastases [7]. Due to the medical history of the patient and the MRI findings, the tumor was considered as highly suspicious for malignancy. Therefore, a whole-body CT scan was performed that excluded recurrent disease in other sites. To the best of our knowledge this is the first case of a late-onset, solitary, deep, soft-tissue metastasis from a pancreatic carcinoma without simultaneous distant spread of the disease to other organs such as the liver or lungs. In the case reported by Horino et al [4], the metastasis to the anterior chest wall developed 8

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months after initial treatment of the disease but was associated with simultaneous liver metastases, whereas in the cases reported by Jun et al [5] and Akasbi et al [6] the metastasis was the first clinical manifestation of a yet unknown primary carcinoma. According to the results of a recent systematic review of 231 deep soft-tissue metastases from a primary carcinoma, the clinical setting of a solitary lesion without further distant organ involvement is common (68.4%), although, contrary to our case, in over 50% of the cases the metastasis is the first clinical manifestation of the disease and not a late-onset phenomenon after successful treatment of the primary malignancy [18].

Considering the good general condition and the symptoms (local pain) of our patient, the favorable location (thigh) and small size of the tumor (less than 4 cm in diameter), and the absence of recurrent disease in additional sites, the decision was taken to perform excisional biopsy of the lesion instead of core needle biopsy. The histopathological analysis of the specimen revealed a metastatic lesion from an adenocarcinoma. Further immunohistochemical analysis was considered unnecessary due to the patient's medical history (known adenocarcinoma of the pancreas).

Although distant metastases of pancreatic adenocarcinoma generally have a poor prognosis, there are insufficient data in the literature on the pathway of evolution, treatment, and prognosis of an isolated, late-onset, soft-tissue metastasis due to the rarity of this entity. In their study of 231 skeletal muscle metastases from primary carcinoma, Pretell-Mazzini et al [18] reported a better mean survival time of patients with single soft-tissue metastasis undergoing surgical excision in comparison to those with unresectable multiple lesions (17.75 months vs 6.7 months), but the difference was not statistically significant and none of the patients had a primary adenocarcinoma of the pancreas. In our case, excision of the lesion in clear margins for diagnostic purposes and to relieve the patients' symptoms and additional chemotherapy seemed to be the ideal treatment option. If this choice will lead also to a prolonged survival remains to be seen, but 8 months later, our patient remains free of disease.

Conclusions

Soft-tissue metastases from a primary carcinoma is a rare entity and in most of the cases the primary malignancy is a lung, kidney, or colon carcinoma. Distant soft-tissue metastases from a pancreatic adenocarcinoma, on the contrary, especially to the subcutis and skeletal muscle, are extremely rare. Although hematogenous spread from pancreatic adenocarcinoma is generally related with a poor prognosis, in very rare cases such ours, of a small, solitary, late-onset (2 years after curative treatment of the primary disease), deep, soft-tissue metastasis, resection of the lesion for diagnostic and palliative purposes and to prolong survival appears to be a reasonable treatment option.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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