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Bone metastasis in follicular dendritic cell sarcoma—a rare site in a rare disease: case report and review of literature

Tsielestina Poulli, Christos Cortas, Antonios Neokleous, Irene Tsappa, Pampina Pilavaki, Morfo Georgiou, Chloe Symeonidou, Nicos Katodritis and Anastasia Constantinidou

***Abstract*:** Follicular dendritic cell sarcoma (FDCS) is a rare sarcoma subtype, presenting as a relatively indolent disease in most cases. Given its rarity, clinicopathological characteristics and behavior as well as treatment, are reported in the literature through case reports and case series. Bone metastasis in FDCS is extremely rare and the outcome of the disease in this group of patients is unknown. We report one case of FDCS with bone involvement as the first site of metastasis. We present the progression of the disease over a period of almost a decade in a detailed manner, particularly the therapies used including immunotherapy with checkpoint inhibitors. In parallel, we provide a comparison with other cases of FDCS metastatic to the bone (total of eight cases) through a systematic review of the literature on the clinical and pathological manifestations as well as the outcomes of all such cases reported to date, to the best of our knowledge. These cases highlight the challenges associated with setting the correct diagnosis at presentation, the lack of evidence to support the role of adjuvant therapy following primary surgery but also the role and/or sequence of systemic options in the advanced setting.

Keywords: bone metastases, case report, follicular dendritic cell sarcoma, soft tissue sarcoma, systemic treatment

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Correspondence to:
Anastasia Constantinidou
Medical School University of Cyprus, Bank of Cyprus Oncology Centre, Department of Medical Oncology, 32 Acropoleos Avenue, Strovolos 2011, Nicosia, Cyprus
Constantinidou.anastasia@ucy.ac.cy

Tsielestina Poulli
Christos Cortas
Antonios Neokleous
Irene Tsappa
Pampina Pilavaki
Medical School University of Cyprus, Strovolos, Nicosia, Cyprus

Department of Medical Oncology, Bank of Cyprus Oncology Centre, Strovolos, Nicosia, Cyprus

Morfo Georgiou
Nicos Katodritis
Department of Radiation Oncology, Bank of Cyprus Oncology Centre, Strovolos, Nicosia, Cyprus

Chloe Symeonidou
Department of Radiation, Bank of Cyprus Oncology Centre, Strovolos, Nicosia, Cyprus

Introduction

Follicular dendritic cell sarcoma (FDCS) is the most common histological subtype among dendritic cell tumors, although a rare sarcoma subtype. Dendritic cells function as antigen-presenting cells, maintaining humoral immune responses. Based on their immunophenotype, the dendritic cell family can be divided into four categories: follicular dendritic cells (FDCs), Langerhans cells, interdigitating cells, and indeterminate cells.[1] FDCs are described as nonphagocytic, nonlymphoid, nonmyeloid cells located in the germinal centers of primary and secondary lymphoid follicles. Tumors originating from FDCs were first suggested by Lennert and Stein[2] in 1978 and described in 1986 by Monda et al.[3] These tumors were named FDCSs in 1994 by Chan et al.[4] A number of reports have documented FDCS cases in the literature, most commonly originating from lymph nodes.[5] FDCS may, however, occur in extranodal tissues from a variety of anatomical sites, including head and neck, liver, spleen, gastrointestinal tract, soft tissue, skin, lung, and breast.[6] According to a pooled analysis of 343 cases of FDCS,[7] median age at diagnosis is 50 years, with males and females affected almost equally (1:1.01). Tumors of the FDCs behave as intermediate-grade sarcomas, with the risk of recurrence and metastasis reported as 21.8% and 27.2%, respectively.[8]

The histological features of FDCS are those of ovoid, polygonal, and spindle-shaped cells forming fascicles and a storiform pattern with whirling.[9] The specific immunohistochemical markers commonly used for the diagnosis of FDCS are

CD21, CD35, and CD23. Other markers that are usually positive include vimentin, EMA, fascin, S100, and CD68.[10] Although the etiopathogenesis of FDCS is unclear, the disease appears to be associated with Castleman disease, representing probably a precursor lesion.[10] Association has also been documented with autoimmune diseases, such as paraneoplastic pemphigus and myasthenia gravis.[7] Finally, the Epstein–Barr virus has been reported to be positive in a variant of FDCS, the "inflammatory pseudotumor-like FDCS."[11]

The treatment of choice for local disease is surgical excision of the tumor which leads to significantly longer overall survival compared to other treatment modalities.[7] The value of systemic therapy—particularly chemotherapy—and radiotherapy in the improvement of survival has not been clearly shown, however, both treatment modalities are included in the management of most cases of metastatic FDCS.[12] In the last few years, response to immune checkpoint inhibitors has also been reported.[13]

Bone metastasis in FDCS patients is extremely rare and the behavior of the disease in this group of patients is unknown. We herein report one case of FDCS with bone involvement as the first site of metastatic disease and present a review of clinicopathological characteristics and outcomes of all cases with bone metastases published in the literature to date, to the best of our knowledge.

Case report

The clinical case managed at our center is one of a 22-year-old man who presented with recurrent episodes of tachycardia, shortness of breath, and dizziness over a period of 2 years, but no abnormal findings on examination, chest X-ray, or blood tests during this period. There was no past medical history of note, the patient was a hairdresser by profession and smoked eight cigarettes per day for 5 years at diagnosis.

In May 2015, a 6.5 cm, solid heterogenous mass of the right superior mediastinum was shown on MRI. A CT-guided biopsy histology showed ovoid cells with a mitotic rate of 1/10 high power field (HPF) surrounded by an aggregate of T and B cells and was positive for CD21 and CD35 setting the diagnosis of FDCS. Staging PET/CT scan confirmed the presence of a mediastinal tumor (SUV max. 5.9) with no other abnormal uptake.

In September 2015, the patient underwent manubriectomy, right anterior thoracotomy, resection of anterior mediastinal tumor, and partial thymectomy for a high-grade, pleomorphic FDCS to an R0 resection. Follow-up imaging studies showed no evidence of recurrence for the subsequent 16 months. In January 2017, however, the patient complained of right hip pain and on MRI a single high signal intensity lytic lesion was demonstrated in the right iliac bone extending to the acetabulum. No other suspicious sites were identified on PET/CT. The lesion was initially attributed to abscess formation with biopsy showing only inflammatory changes and was therefore treated with IV antibiotics but with minimal response. As the pain persisted, in August 2017, he proceeded to have complete resection of the lesion followed by cementoplasty and as suspected the pathology findings this time, were consistent with FDCS. On staging with MRI, four further bone lesions were identified (left pubic bone lesion, left acetabular lesion, and bone lesions at the level of T8 and T11). Small-size mediastinal lymphadenopathy at the site of the primary operation was also noted. The patient received six cycles of chemotherapy comprising ifosfamide and Doxorubicin as per clinical guidelines for first-line systemic treatment for soft tissue sarcoma[14] between October 2017 and January 2018 with good tolerance and symptomatic improvement and stable disease according to the Response Evaluation Criteria In Solid Tumours (RECIST) criteria.

He remained symptomatically fairly well on bisphosphonates and close follow-up for a period of approximately 18 months with the bone metastases remaining largely stable but small volume lung metastases and mediastinal lymphadenopathy appearing by the end of 2019. He received external beam radiotherapy to the mediastinal lymphadenopathy in February 2020, achieving partial response. As he developed symptomatic progression due to new metastatic bone disease in the left acetabulum, he received palliative radiotherapy at that site in August 2020. He remained clinically stable, continuing on zoledronic acid alone and maintaining a good quality of life until January 2021.

He then presented with disease progression largely in the skeleton but also in the lungs and mediastinum. He received systemic treatment with trabectedin (March 2021–September 2021)[15] but in October 2021 he had further progression in the left iliac bone and he developed a

symptomatic left-sided pleural mass, he therefore received radiotherapy to both sites. Following a short period of symptomatic stability, progression in the thoracic spine (level T1 and T9), the pleura, the lungs, and an increase of the mediastinal and hilar lymphadenopathy, were documented in early 2022. The patient received palliative radiotherapy to the thoracic spine sites and systemic chemotherapy with six cycles of gemcitabine and docetaxel achieving a partial response in the pleural and lung metastases as well as the mediastinal lymphadenopathy.[16] Bisphosphonates were switched to denosumab.

In January 2023, the disease progressed further with an increase in lymphadenopathy above and below the diaphragm but also liver metastases for the first time. The patient was evidently more symptomatic and of ECOG performance status 1. Based on case reports of response of FDCS to immunotherapy the patient was set on Ipilimumab and Nivolumab, starting in February 2023. He received four cycles of Ipilimumab and Nivolumab and then remained on Nivolumab maintenance therapy. In the first response assessment CT scan 3 months later, he had an impressive partial response at all involved sites and the disease remained under control with excellent quality of life, for a period of 1 year.[13] The best radiological response is presented in Figure 1. The similarities of FDCS to hematological malignancies provide anecdotal evidence for the utilization of chemotherapy regimens used in non-Hodgkin's lymphoma. Along this paradigm, in April 2024 the patient commenced chemotherapy with cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) due to documented progression of the lymphadenopathy above and below the diaphragm as well as the pleural disease.[17] Bone metastases remained stable. Following three cycles of therapy, partial response by RECIST was achieved in the hilar and axillary lymphadenopathy as well as the pleura.

Materials and methods

A PubMed database search was conducted using the keywords "follicular," "dendritic," "cell," "sarcoma," and as of April 29, 2024, the search results identified 648 records (Figure 2). From the 648 records screened, we isolated those reporting one or more clinical cases of patients with FDCS. Records of cases with Castleman disease and pseudotumor-like FDCS were excluded. Three hundred forty-eight (348) articles were assessed by screening article titles and abstracts for the detection of cases with metastatic bone involvement. Reference articles mentioning FDCS cases were screened for additional clinical cases fulfilling our criteria. Seven articles including eight cases of FDCS metastatic to bone were identified in the English literature, constituting a total of nine cases including our own. The nine cases are described in terms of clinicopathological characteristics, management, and course of disease. The reporting of our case report conforms to the CARE guidelines[18] (Supplemental File).

Results

The demographic and clinicopathological characteristics, treatment strategies, recurrence patterns, and the outcome of all eight identified cases and our case reported in this work, are described below in detail and presented in Table 1.

Two of the eight identified cases are described by Grogg et al.[19] The first refers to a 14-year-old male whose initial site of disease was a right cervical lymph node. The tumor cells were spindle shaped and stained positive for CD68, fascin, clustern, EMA, and factor XIIIa. The disease recurred multiple times over 30 years, specifically in L2–L3 vertebral bodies, right adrenal gland, right parotid, and occipital soft tissue. The treatment strategy included multiple resections and radiotherapy to the lumbar spine. At the time of the report, the patient was alive with the disease 30 years post-diagnosis.

The second case was that of a 26-year-old woman with FDCS first detected at the right cervical lymph node with multiple recurrences in the right supraclavicular fossa, rib, T9 vertebral body, iliac bone, and left cervical lymph nodes. The cells on electron microscopy stained positive for CD68, fascin, clusterin, and EMA. The initial treatment for this patient included chemotherapy comprising methotrexate, cisplatin, and adriamycin. During the recurrences, the patient underwent radiotherapy and received chemotherapy with ifosfamide. At the time of the report, the patient was alive with the disease, 5 years post-diagnosis.

The third case was reported by Jiang et al.[20] and referred to a 46-year-old woman who presented with a large mass in the upper mediastinum, giving rise to right upper limb pain and swelling. The mass was initially misdiagnosed as diffuse large B-cell lymphoma and the patient received six

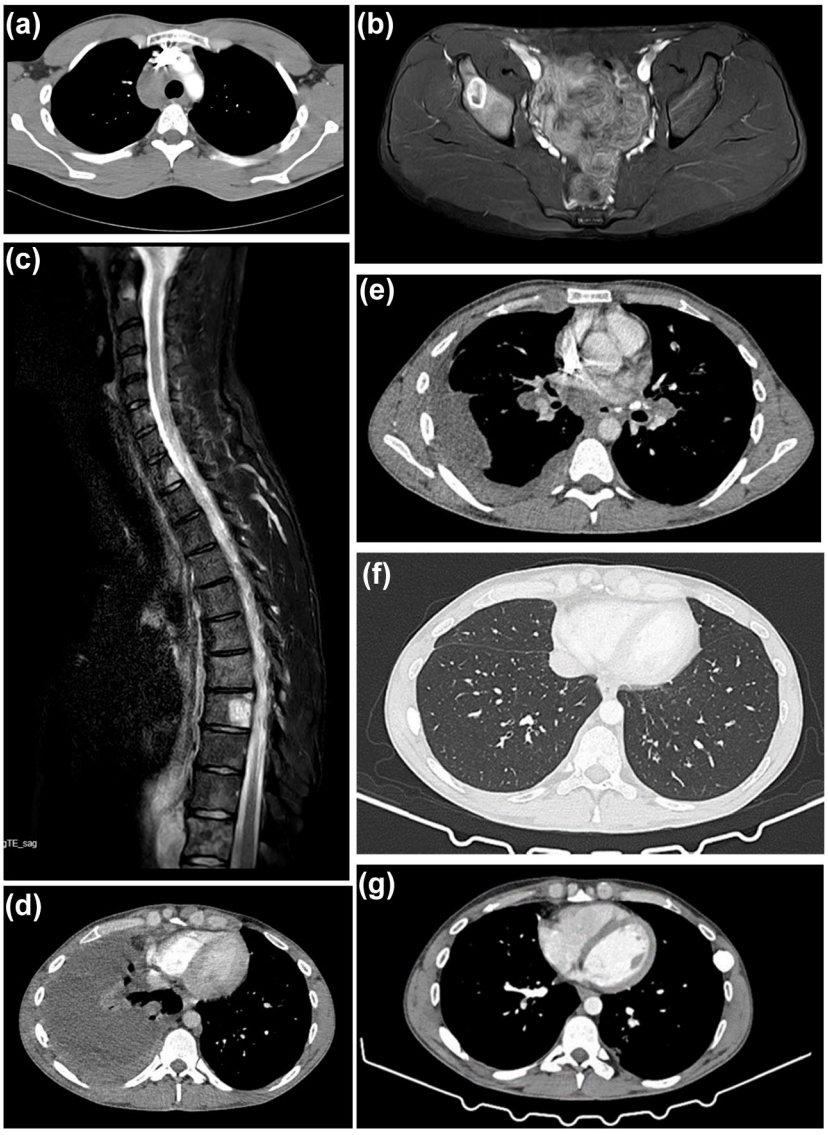

Figure 1. (a) CT chest at diagnosis: low-density lesion in upper mediastinum adjacent to trachea. (b) MRI of pelvis at first recurrence: high signal intensity involving right iliac bone extending also to the area of the articular surface of acetabulum. This lesion was primarily diagnosed as abscess formation, based on radiological findings. However, biopsy of the lesion set the diagnosis of metastasis from FDCS. (c) MRI of cervical and thoracic spine: multiple osseous lesions in C2, T1, and T9 that are suggestive of secondary deposits. There is no evidence of spinal cord compression. (d, e) CT chest at baseline before the start of immunotherapy: increased pleural thickening in the right lung and pleural effusion with overlying compressive atelectasis. Mediastinal and hilar adenopathy. (f, g) CT chest at the time of best response during immunotherapy: significant decrease in the size of subpleural lesion on the right lung. In addition, a decrease in the size of hilar and mediastinal lymphadenopathy.
FDCS, follicular dendritic cell sarcoma.

cycles of R-CHOP. FDG/PET CT showed persistent disease, so the patient received two cycles of ESHAP and adjuvant radiotherapy. The diagnosis of FDCS was established after the patient presented with hip pain due to multiple lytic lesions in the pelvic bones and a large (5 cm) mass on the left sacrum. The excisional biopsy of the sacral mass showed similar characteristics to those of the mediastinal mass, which were diffuse infiltration of ovoid or polygonal cells forming fascicular arrays. The immunohistochemistry of the mediastinal mass revealed positivity for CD21, CD23, CD35, EGFR, and clusterin. Total surgical excision of all disease sites was not

performed because of tumor location and infiltration of adjacent organs. Thus, the patient received six cycles of gemcitabine and docetaxel with symptomatic and imaging improvement. One month after treatment completion, the patient showed no FDCS in bone marrow biopsy. However, she presented with disease progression 6 months later and received high-dose methotrexate with cytarabine, ifosfamide, and VP-16. The patient was alive with disease at the time of the report, 2 years post-diagnosis.

A review of the extranodal FDCSs,[21] reported the case of a 23-year-old man with an 8 cm mediastinal FDCS, which was initially diagnosed as malignant peripheral nerve sheath tumor (MPNST). The tumor cells stained positively for CD21, CD23, CD35, CD68, S100, p53, and vimentin. The histological specimen showed 3 mitotosis/10 HPF. The initial treatment comprised a combination of surgery, radiotherapy, and chemotherapy, but the disease recurred with distant metastasis in the skeleton 45 months after the surgery. The patient was alive with disease at the 45-month follow-up timepoint. The report did not provide further information on the location and the management of osseous lesions.

In the fifth case,[22] bone diseases were discovered initially along with enlarged lymph nodes in the hilum of the left lung. The 36-year-old female patient presented with recurrent fever and abdominal pain for 20 days and after the detection of multiple bone lesions, a biopsy in the left iliac bone revealed hyperplastic epithelial-like cells with double or multiple nuclei and sporadically spindle cells. The cells stained positive for CD35, C68, CD163, S100. The symptoms improved after 12 cycles of chemotherapy and the patient was stable in the 2-year follow-up.

In a 2015 case report and review of the literature[8] a case of a 24-year-old man was presented. He complained of intermittent pain in multiple bones (thorax, lumbar vertebrae, and ribs) for 2 months and was diagnosed with FDCS in the spine, ribs, shoulder blade, and other bone sites and in lymph nodes (axillary and supraclavicular). Biopsy of the left cervical lymph node showed tumor cells arranged in a wispy and storiform pattern with positive immunohistochemical staining for CD21 and CD35. Based on multiple-site disease involvement the patient did not undergo surgical treatment. The patient's disease and symptoms completely disappeared after four cycles of

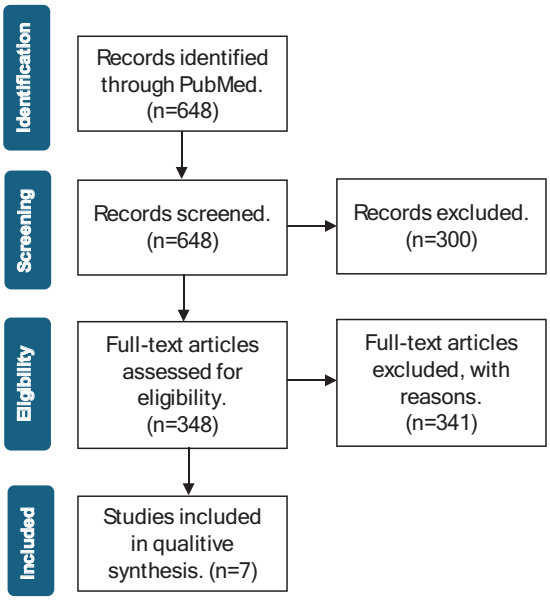

Figure 2. PRISMA 2009 flow diagram.

etoposide plus cisplatin and to strengthen the treatment outcome the patient also received six cycles of CHOP. He responded well to the treatment and had a radiologic complete response. The patient did not have any evidence of recurrence during a 9-year follow-up.

The seventh presented FDCS case with bone involvement[9] referred to a 45-year-old male patient who presented with a 4-month history of right mandibular numbness, pain, and weight loss. The MRI showed a lesion in the body of the mandible and the patient underwent dental extraction, wide local excision, and curettage of the cyst epithelium. The pathology showed rounded cells in fascicular and whorled pattern, which stained positive for CD21, clusterin, CD35, and CYCL13. With the uptake in the PET/CT scan in the mandibular ramus, the patient underwent a right composite hemimandibulectomy with selective right-sided neck dissection. The patient did not receive any further treatment and had no evidence of recurrence after 1 year of follow-up.

In 2022, Hu et al.[23] presented a case of a 36-year-old male patient with FDCS in the thoracic spine who sought medical attention due to deteriorating pain in the left scapula over 6 months. Imaging with CT showed soft tissue neoplastic lesions on the left side of C7–T2 vertebrae, invading the body of T1 and T2 and caput costae of the

Table 1. Summary of clinical data from cases with FDCS and bone metastases.

Case	Sex	Age at diagnosis	Symptoms	Site of tumor at presentation	Biopsy/immunophenotype	Treatment	Recurrence	Treatment of recurrence/palliative	Outcome
Grogg et al.[19]	M	14	NA (non applicable)	Right cervical lymph node	Spindle-shaped tumor cells with long intertwining processes. Positive for CD68, Fascin, clusterin, EMA, Factor XIIIa Negative for CD21, CD23, CD35, CD1a, S-100, Actin, Desmin, AE1/3, CAM5.2, ALK-1	Multiple resections, radiotherapy (RT) to lumbar spine	Multiple recurrences over 30 years in L2–L3 vertebral bodies, right adrenal, right parotid, occipital soft tissue	Multiple resections, RT to lumbar spine	Alive with disease in 30 years follow up (FU)
Grogg et al.[19]	F	26	NA	Right cervical lymph node (LN)	EM: spindle-shaped tumor cells with long intertwining processes connected by well-formed desmosomes Positive for CD68, Fascin (focal staining), clusterin (strong staining), EMA, Negative for CD21, CD23, CD35, CD1a, S-100, Actin, Desmin, AE1/3, CAM5.2, ALK-1, Factor XIIIa	Methotrexate, cisplatin, adriamycin	Multiple recurrences over 5 years in R supraclavicular LN, rib, T9 vertebral body, iliac bone, L cervical LN	RT × 4 times, ifosfamide	Alive with disease 5 years FU
Jiang et al.[20]	F	46	Right shoulder pain and swelling in the right upper extremity, left gluteal pain	Mediastinum (initial diagnosis as diffuse B-cell lymphoma)	Mediastinal mass: diffuse infiltration of ovoid or polygonal cells forming fascicular arrays with a vaguely storiform pattern in some areas. No coagulative necrosis. Mitotic count: 9 per 10 HPF Positive for CD21, CD23, CD35, EGFR, clusterin, vimentin Negative for CD45, CD30, CD20, CD10, CD5, CD1a, TdT, S-100, keratin cocktail, CD138, desmin	At first diagnosed as diffuse B-cell lymphoma R-CHOP, ESHAP, and rituximab, radiotherapy	Two recurrences Bone metastasis (pelvis, sacrum) with bone marrow involvement	Chemotherapy gemcitabine and docetaxel, high-dose methotrexate with cytarabine, ifosfamide, and VP-16	Alive with tumor in 2 year follow-up
Li et al.[21]	M	23	NA	Mediastinum (initial diagnosis as MPNST)	8 cm, low histological grade, 3 mitoses/10 HPF Positive for Vimentin CD21, CD23, CD35, Podoplanin CD68, S-100 protein, p53 protein1, Ki-67-LI, 15% EBER Negative for CK, EMA, CD45	Surgery, radiotherapy, chemotherapy	Bone metastasis	Surgery, radiotherapy, chemotherapy	Alive with disease in 45 months FU
Jiang et al.[22]	F	36	Recurrent fever and abdominal pain for 20 days	Multiple bones, lymph node in the left hilum of the lung	Hyperplastic epithelial-like cells with double nuclei or multiple nuclei, and sporadically spindle cells. Positive for CD35, CD68, CD163, S-100, Ki-67, LYSO, LCA Negative for CD1a, CD4, CD21, CD56	Chemotherapy	No	–	Stable after 2 year follow-up

(Continued)

Table 1. (Continued)

Case	Sex	Age at diagnosis	Symptoms	Site of tumor at presentation	Biopsy/immunophenotype	Treatment	Recurrence	Treatment of recurrence/palliative	Outcome
Ma et al.[8]	M	24	Intermittent pain in multiple bones	Multiple enlarged lymph nodes in the bilateral axillary, supraclavicular area, multiple bone metastasis (spine, ribs, shoulder blade, and others)	Positive for CD21, CD35, vimentin, D2-40 Negative for CD23, cytokeratin, CD20, CD30, CD117, S-100, epithelial membrane antigen, CD45, CD68, D2-40, EBER	Chemotherapy (Etoposide + cisplatin → good response, CHOP)	No	–	Stable after 9 years follow-up
Pang et al.[9]	M	45	4 months of right mandibular numbness and pain, and unintentional 10-pound weight loss	Mandible	Cystic lesion of dense aggregates of rounded cells in a fascicular and whorled pattern mixed with lymphocytes. Positive for clusterin and CD21, partially positive for CD35 and CXCL13, and negative for p63, CK5, S100, MART-1, Melan-A, LCA, kappa, lambda, CD3, CD30, CD138, CD163, Alk-1, OSCAR, MUM-1, PAX5, CD4, CD2, and CD43	Surgery: Right composite hemimandibulectomy with a right selective neck dissection of levels I–IV	No	–	No recurrence in 1 year FU
Hu et al.[23]	M	36	Worsening pain in the left scapula	Paraspinal mass at the level of C7-T2, infiltrating T1–T2 vertebrae and caput costae of left second rib. Single metastasis in left iliac bone	Diffuse small spindle cells. Positive for CK and vimentin, partially positive for CD68 and EMA; slightly positive for S100 and CD34; and negative for Sox10, Langerin, TTF-1, and PSAP	Tumor resection and body gamma knife	No		Alive, without recurrence, 15 months on follow-up
Our case report	M	23	Difficulty with breathing, tachycardia, episodes of dizziness and weakness	Mediastinum	Ovoid cells forming whorls, mitotic rate 1 per 10 HPF, surrounded by aggregates of T and B lymphocytes. Positive for CD21, CD35 Negative for CD23, CD1a, S-100, CD20, CD79a, CD3, PAX5, CD30, CD15, CD68, CD34	Surgery	Bone metastasis	Ifosfamide and Doxorubicin, zoledronic acid, radiotherapy, trabectedin, gemcitabine/ docetaxel, ipilimumab/ nivolumab, CHOP	Alive with disease 9 years, clinical progression

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; FDCS, follicular dendritic cell sarcoma; MPNST, malignant peripheral nerth sheath tumor.

second left rib. A synchronous metastatic lesion was located in the left iliac bone. The patient underwent tumor resection and nerve root decompression of the primary site and then received body gamma knife radiation, as adjuvant treatment at the primary site and as radical treatment of metastatic disease. No systemic treatment was administered. A CT scan 2 months post-surgery showed a slight increase in the size of the bone lesion, therefore an iliac bone resection was performed confirming pathologic complete response. The patient had no evidence of recurrence after 15 months of follow-up.

Discussion

We herein presented the clinical, pathology, and treatment data for all cases with FDCS and associated bone metastases, as reported in the literature to date. A pooled analysis of 343 cases of FDCS, one of the largest series to date, showed that the most common sites of metastases are the lung, lymph nodes (around half of the patients[7]), and liver, with a 2-year survival rate for distant metastatic disease being 42.8% compared to 82.4% in early disease.[7] In general, the majority of patients survive up to 10 years and beyond.[9] Factors associated with poor prognosis include tumor size (⩾6 cm), presence of coagulative necrosis, high mitotic count (⩾5 per 10 HPF), absence of lymphoplasmacytic response, and significant cytological atypia.[7] Patients diagnosed in younger age (<40 years), with intra-abdominal involvement and having combined nodal/extranodal involvement are reported as having a trend for poorer prognosis but without statistical significance.[7]

In this review of cases of FDCS with bone metastases, particular demographics were similar to those of other cases with FDCS. The age at diagnosis ranged from 14 to 46 years, which is somewhat lower than the median age for FDCS reported as 50 years.[5,7] The majority of the patients had bone-related pain at the presentation. Three of the cases initially presented with metastatic disease in the bones, while for the rest of the patients, bone metastases appeared later in the course of their disease.

Notably, the location of the primary site was the mediastinum in three out of eight cases—as was the primary tumor location in our patient—while in four other cases lymphadenopathy was the only or one of the main features at presentation. Interestingly, two cases were initially misdiagnosed, one as diffuse B-cell lymphoma and another one as MPNST which highlights—the well-recognized—challenge of setting the correct diagnosis in rare malignancies such as sarcoma, particularly in the cases of very rare subtypes such as FDCS. In our patient's case, there was a delay in identifying the original tumor in the mediastinum, despite the fact the patient reported episodes of tachycardia, shortness of breath, and dizziness for a period of 2 years prior to diagnosis. Consequently, the size of the primary tumor at surgery was over 6 cm.

The therapeutic strategies followed for the treatment of the eight patients were surgery alone, surgery with radiotherapy, surgery with chemotherapy, surgery with chemotherapy and radiotherapy, and chemotherapy alone for four patients. In addition, the radiotherapy and chemotherapeutic regimens used varied both in terms of timing of administration and type/dose of treatment. This variation in therapeutic approaches is due to the lack of evidence-based recommendations for optimal management, owing primarily to the rarity of the disease. Complete surgical resection is the treatment of choice for localized disease but there is no established role for adjuvant radiotherapy or chemotherapy. Our patient underwent a complete (R0) resection in a large sarcoma center in the UK and in view of the R0 resection and the absence of evidence to support radiotherapy, he did not receive adjuvant radiotherapy to the primary site. The course of FDCS is considered indolent but approximately half of the patients will develop locoregional recurrence while some will present with aggressive metastatic disease which may be underestimated for many years.[8,13,24,25]

With regards to systemic therapy, there is no optimal regimen or sequence of chemotherapy or targeted therapy to treat FDCS and ultimately the management is based on retrospective data from case reports and case series. The combination of doxorubicin and ifosfamide administered as first-line treatment did not achieve an objective response but did help with symptomatic improvement and perhaps contributed to a slow subsequent disease progression. Of the subsequent lines of systemic therapy, the combination of gemcitabine and docetaxel resulted in partial response along the lines of other reported series' outcomes[24]; which however lasted for less than 6 months. What was impressive in our patient's

journey was the response to the combination of nivolumab and ipilimumab, which not only achieved the best objective response since the diagnosis of metastatic disease but also gave the patient 1 year of excellent quality of life. The response of FDCS to immunotherapy has been reported in several case reports,[26,27] although the low tumor mutational burden argues against its efficacy in this mesenchymal subtype.[28] Finally, traditionally, FDCS was often treated with anthracycline-based lymphoma chemotherapy regimens (CHOP, ABVD, and ICE) but the response has been variable.[29,30] Our patient is currently undergoing such therapy and indeed interim assessment has shown partial response to therapy.

The role of radiotherapy in FDCS is also unclear but what we noted was that the extensive bone disease in our patient responded well to palliative radiotherapy allowing him long periods of pain-free time avoiding continuous therapy with chemotherapy. Bisphosphonates may have contributed as well.

The presentation of this case is limited by its retrospective nature and its extreme rarity. FDSC is reported as 0.4% of soft tissue sarcomas, which represent approximately 1% of all malignancies. The percentage of FDCS patients with bone metastases is yet to be defined. The systematic review, included in this article, produced only eight more cases of FDCS with bone metastases up until April 2024, thereby limiting significantly any attempt to draw definitive conclusions on the superiority of one regimen over another.

Our young patient has been fully informed of the status of his rare malignancy at every step of the disease, since diagnosis. He has demonstrated admirable courage and perseverance through disease progression and by providing consent for this publication he confirms his wholehearted support in spreading this knowledge for the potential benefit to others.

Conclusion

Bone is an extremely rare site of metastasis of FDCS, and in this presentation, we report the characteristics, the course of disease, and the response to treatment of eight such cases alongside our case. Even though this review presents all cases of bone metastases from FDCS published in the literature to date, due to the small number of cases available, the extraction of definitive conclusions is not possible. However, through the cumulative description provided in this study, demographic, clinicopathological characteristics, different treatment strategies, and outcomes are available for comparison and for future reference in practice.

The preferred treatment approaches vary according to the extent and location of the disease, with both radiotherapy and systemic therapy (chemotherapy, immunotherapy) being valuable, as all patients, including ours, were either alive with the disease or showed no signs of recurrence during the follow-up. A larger scale, detailed series of such rare cases is required to allow a better understanding of the behavior of the disease and its response to therapy.

Declarations

Ethics approval and consent to participate

According to internal institutional policies, ethics approval is not required for the present study. An informed consent was obtained for the publication of this report and any accompanying clinical data including images. Consent to participate: written informed consent was obtained by the patient.

Consent for publication

Written consent for publication was provided by the participant.

Author contributions

Tsielestina Poulli: Data curation; Formal analysis; Methodology; Writing – original draft; Writing – review & editing.

Christos Cortas: Data curation; Methodology; Validation; Writing – review & editing.

Antonios Neokleous: Data curation; Investigation; Writing – review & editing.

Irene Tsappa: Data curation; Investigation; Writing – review & editing.

Pampina Pilavaki: Data curation; Investigation; Writing – review & editing.

Morfo Georgiou: Data curation; Formal analysis; Writing – review & editing.

Chloe Symeonidou: Data curation; Formal analysis; Writing – review & editing.

Nicos Katodritis: Conceptualization; Writing – review & editing.

Anastasia Constantinidou: Conceptualization; Data curation; Methodology; Resources; Supervision; Validation; Writing – review & editing.

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Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
All data on case report presented in this article are available upon request.

ORCID iD
Anastasia Constantinidou https://orcid.org/0000-0001-5316-7574

Supplemental material
Supplemental material for this article is available online.

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