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① Multidisciplinary treatment including sorafenib stabilized the bone metastases of renal cell carcinoma in an immunosuppressed renal transplant recipient.

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CASE REPORT

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Multidisciplinary treatment including sorafenib stabilized the bone metastases of renal cell carcinoma in an immunosuppressed renal transplant recipient

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Abstract We report a case of metastatic renal cell carcinoma in the native kidney of a renal transplant recipient. The patient was a 57-year-old man in whom a tumor in the native kidney and bone metastasis were found incidentally on imaging, 10 years after cadaveric renal transplantation. Interferon-alpha was administered after nephrectomy and following palliative irradiation of the metastasis, but could not be continued because of allograft dysfunction. Subsequent administration of zoledronic acid and sorafenib stabilized the disease for 18 months after nephrectomy. This is the first reported case of sorafenib administration to a renal transplant recipient with metastatic renal cell carcinoma.

Key words Renal cell carcinoma · Renal transplantation
Sorafenib · Zoledronic acid

Introduction

The incidence of renal cell carcinoma (RCC) of the native kidney in patients who have undergone renal transplantation is about 10 to 100 times greater than that in the general population.[1-4] Metastasis at diagnosis occurs in fewer than 10% of all cases of RCC arising in the native kidney after renal transplantation, but the prognosis of such cases is extremely poor.[1,3,5] Immunotherapy is theoretically contraindicated for patients receiving immunosuppressive therapy (IST), but some investigators have reported successful treatment of metastatic RCC (mRCC) and hepatitis C using interferon-alpha (IFN) in renal transplant recipients.[6,7]

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In the renal transplant recipient with mRCC we report here, IFN was administered after nephrectomy and following palliative irradiation, but could not be continued due to allograft dysfunction. Subsequently, the administration of zoledronic acid and sorafenib to this patient with bone metastatic RCC led to stable disease for 18 months after the nephrectomy. Zoledronic acid has previously been administered to renal transplant recipients for the prevention of bone mineral density loss, without the occurrence of serious adverse events;[8] however, there are no previous reports of sorafenib administration to patients with mRCC who have received IST. Therefore, our case is the first successful treatment of RCC with bone metastasis using sorafenib in a renal transplant recipient.

Case report

The patient was a 57-year-old man in whom a tumor was found incidentally in the right native kidney and bone metastasis was discovered in the right acromion and ninth thoracic vertebra by computed tomography (Fig. 1a, b, c), magnetic resonance imaging, and bone scintiscan, 10 years after cadaveric renal transplantation. Retroperitoneoscopic radical nephrectomy was performed, and a histological examination demonstrated RCC (clear cell carcinoma, grade 2, pT3a). Administration of IFN (3 MU s.c. three times a week) and palliative irradiation for bone metastasis (50 Gy to the vertebra and 54 Gy to the acromion) were started. Eighteen days after the first administration of IFN, the patient complained of high fever, right groin pain, and oliguria, and allograft dysfunction occurred. We suspected allograft rejection, and a percutaneous needle biopsy of the allograft was performed, but rejection was unclear histologically. Pyelonephritis was diagnosed, then IFN was discontinued and antibiotics were initiated. Renal function and other clinical signs recovered gradually, and 42 days after the first administration of IFN we tried to resume administration of IFN (3 MU s.c. twice a week). However, allograft dysfunction and high fever recurred 53 days after the second

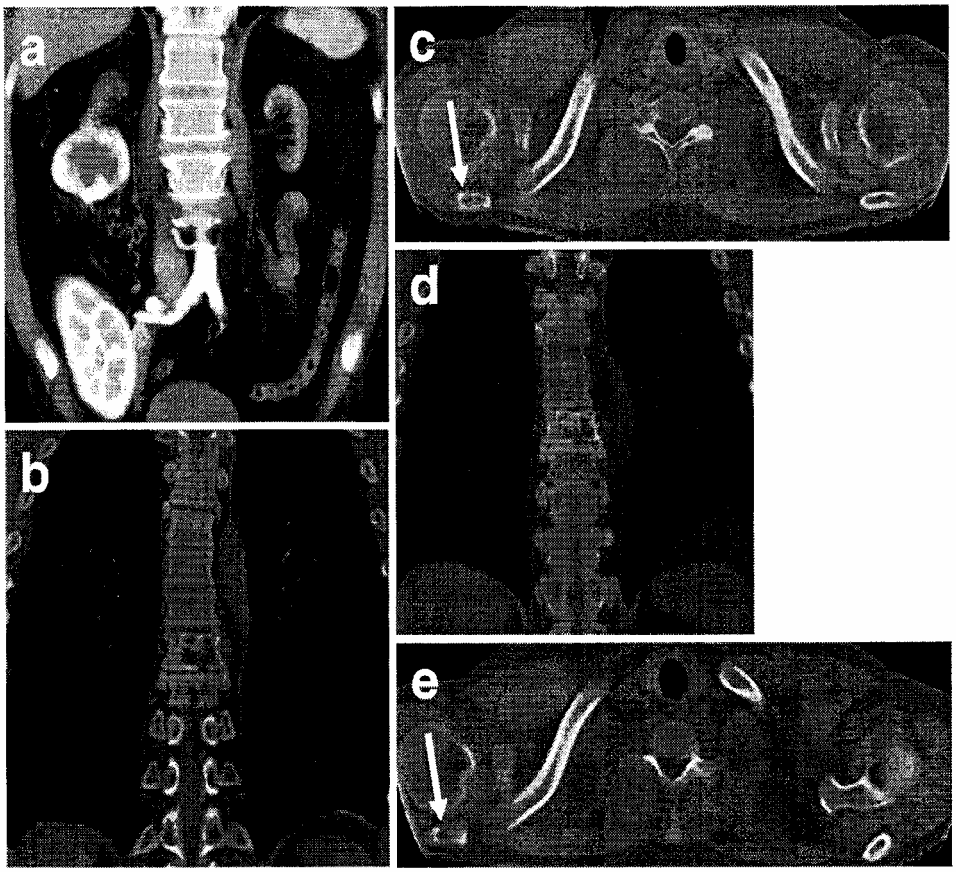

Fig. 1a–e. Computed tomography (CT) revealed a renal tumor in the right native kidney (**a**) and bone metastasis in the ninth vertebra (**b**) and the acromion (**c**). CT showed no sign of disease progression at metastatic sites 18 months after nephrectomy (**d, e**)

administration and IFN could not be continued. Therefore, zoledronic acid was administered (4 mg i.v. every month).

About 3 months after the surgery, we discovered that the patient had purchased sorafenib (Nexavar; Bayer HealthCare Pharmaceuticals, West Haven, CT, USA and Onyx Pharmaceuticals, Emeryville, CA, USA) by self-import from the United States, and that he had begun to take sorafenib orally at a dose of 200 mg every other day from 68 days after the nephrectomy, based on his own decision and without our permission. Allograft dysfunction occurred 107 days after the nephrectomy, and we convinced him to stop taking sorafenib. After his renal function recovered, on day 215 after the nephrectomy, we permitted the taking of sorafenib orally at the same dose as before, based on informed consent. No serious adverse events occurred during the subsequent 11 months while the patient was taking sorafenib, and there has been no evidence of disease progression for 18 months after the nephrectomy (Fig. 2).

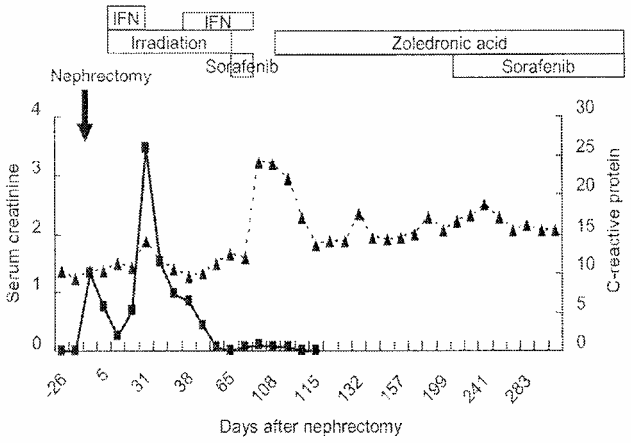

Fig. 2. Clinical course: serial profiles of serum creatinine (*triangles*) and C-reactive protein (*squares*) before and after treatment. *IFN*, interferon

Discussion

In the latest studies, about half of the RCC cases in renal transplant recipients are high-grade and the majority are early-stage, and these studies suggest that the short-term prognosis is favorable after radical surgery, even for transplant recipients with a high-grade tumor.[1,3,5] However, patients with metastatic disease at diagnosis have died of RCC within 2 to 4 months of diagnosis.[3,5] The standard surgical treatment for RCC arising in the native kidney is radical nephrectomy;[9] however, to our knowledge, there are no recommendations in the literature concerning adjuvant therapy for mRCC arising in the native kidney in patients receiving IST.

New antiangiogenesis agents with proven efficacy and tolerance in patients with mRCC have recently been approved in many countries, and these drugs have had a

marked effect on the treatment strategy for mRCC. In fact, European Association of Urology (EAU) guidelines on mRCC include no recommendations for cytokine therapy, except in selected patients, and sunitinib, temsirolimus, and sorafenib are considered as first- or second-line systemic therapy for mRCC.[10] Immunotherapy is theoretically contraindicated for patients receiving IST. Interleukin-2 should not be administered to such patients because the IST for the prevention of allograft rejection contains an interleukin-2 antagonist, such as cyclosporin. In addition, IFN has been associated with a high incidence of allograft dysfunction or acute rejection,[11] although the safety and effectiveness of IFN in renal transplant recipients has also been reported.[6,7]

RCC has historically been considered to be unresponsive to radiation therapy (RT) based on in vitro experiments.[12] At present, the main role of RT for patients with mRCC is for the palliation of symptomatic bone metastases; however, some retrospective studies have reported good clinical responses to RT in the setting of mRCC.[13] Zoledronic acid is a bisphosphonate that reduces the risk of skeletal-related events in patients with solid tumors, including RCC with bone metastasis.[14,15] Haas et al.[8] showed that administration of zoledronic acid prevented bone mineral density loss in renal transplant recipients and that renal function did not change significantly after zoledronic acid infusion. Sorafenib is a multikinase inhibitor with effects on tumor cell proliferation and tumor angiogenesis.[16] In mRCC, a phase III trial comparing sorafenib and placebo after the failure of prior systemic immunotherapy showed a 24-week median progression-free survival with sorafenib compared with 12 weeks for patients receiving the placebo ($P > 0.000001$). After 3 months of treatment, 75% of the patients taking sorafenib were progression-free compared to 43% of those taking the placebo.[17] In vitro and in vivo data indicate that sorafenib is primarily metabolized by the liver; however, in a study of drug disposition after a single oral dose of radiolabeled sorafenib to healthy subjects, 19% of the administered dose of sorafenib was excreted in urine. The pharmacokinetics of sorafenib have not been studied in patients with severe renal impairment (creatinine clearance, less than 30 ml/min) including dialysis patients and renal transplant recipients.[18] To our knowledge, there are no previous reports of the safe use and effectiveness of sorafenib for immunosuppressed renal transplant recipients with mRCC.

In our patient, zoledronic acid and sorafenib were administered after allograft dysfunction that was probably induced by IFN. For 16 months after the patient began taking sorafenib, based on informed consent, there has been no evidence of disease progression and there have been no severe adverse events. Therefore, this case may indicate the efficacy and tolerance of RT, zoledronic acid, and sorafenib in patients with bone metastatic RCC who have undergone renal transplantation.

In conclusion, we have reported a patient with bone metastatic RCC who received IST and was then successfully treated with RT, zoledronic acid, and sorafenib. This combination therapy for RCC with bone metastasis may be safe and effective in immunosuppressed renal transplant recipients, and we suggest that further investigation of sorafenib is warranted in this patient population.

Conflict of Interest Statement

No author has any conflict of interest.

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① First report of liposarcoma of the spermatic cord after radical prostatectomy for prostate cancer.

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④ Anticancer Research

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First Report of Liposarcoma of the Spermatic Cord after Radical Prostatectomy for Prostate Cancer

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Abstract. *Primary liposarcoma of the spermatic cord (LSC) is a rare neoplasm; there are fewer than 100 cases reported in the English literature worldwide. A seventy-one year-old man, who had undergone radical retropubic prostatectomy (RRP) for localized prostate cancer in November 2004, noticed the enlargement of a mass in the left scrotum. Subsequently he underwent a biopsy of the lesion, which documented suspicion of leiomyosarcoma of the spermatic cord. Left radical orchiectomy was performed extending to the resection margin. The pathological examination showed a dedifferentiated liposarcoma of the left spermatic cord. To the best of our knowledge, this is the first report of LSC after RRP for prostate cancer in the English literature.*

Radical retropubic prostatectomy (RRP) is a standard treatment option for clinically localized prostate cancer. Inguinal hernia is one of the major morbidities after RRP since its incidence is 6.7% to 21% (1, 2). From speculations in previous reports, certain kinds of manipulation during RRP that can weaken or distort the normal fascia structure at the internal inguinal ring, including incision and retraction of the transversalis fascia with a retractor, stretching of the vas deferens and incision of the endopelvic fascia, may have an important role (2). The pathogenesis of inguinal hernia after RRP is still largely unknown.

Liposarcomas of the spermatic cord (LSCs) are rare tumors. Liposarcomas are malignant neoplasms of adipose tissue arising from primitive mesenchymal cells. In almost 70% of cases they are located in the extremities and the retroperitoneum. The spermatic cord is a rare site of origin, accounting for about 3-7% of all liposarcoma (3). The first case of LSC after RRP for prostate cancer is reported here.

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Key Words: Liposarcoma, spermatic cord.

Case Report

A 71-year-old man noticed the enlargement of a mass in the left hemiscrotum for more than five months. He had undergone RRP for localized prostate cancer in November 2004. The pathological findings of the prostate had been Gleason sum 3+4=7, pT2a and negative margins. In February 2008, the serum prostate-specific antigen (PSA) level was 0.057 ng/ml and neither biochemical failure nor recurrence was confirmed. Computed tomography (CT) revealed a 35×25 mm low-density round mass in the left spermatic cord. Magnetic resonance imaging (MRI) showed a smooth margined low-intensity mass on T1- and T2-weighted image, which involved the epididymis and left spermatic cord (Figure 1). Subsequently the patient underwent a biopsy of the lesion. The pathology of the biopsy specimen was suspicious of leiomyosarcoma of the spermatic cord. In April 2008, left radical orchiectomy was performed extending to the resection margin. Macroscopically, the lesion was a capsulated mass (95×55 mm) composed mostly of adipose tissue infiltrating the spermatic structures (Figure 2). The pathological examination showed a well-differentiated liposarcoma which revealed fat cells and lipoblasts, and a dedifferentiated section which revealed spindle cells having atypical highly multiplied nuclei like a myxofibrosarcoma (Figure 3), and resulted in negative margins. There was no evidence of recurrence on CT and physical examination four months after surgery.

Discussion

The present case underwent conventional RRP and suffered from liposarcoma of the spermatic cord (LSC) beside the inguinal region, not an inguinal hernia, four years after prostatectomy. To date, the relationship between tumorigenesis of LSC and the RRP procedure which has some impact on the inguinal canal and inguinal region seems to be unclear, and no cases of LSC after RRP have been reported in the English literature.

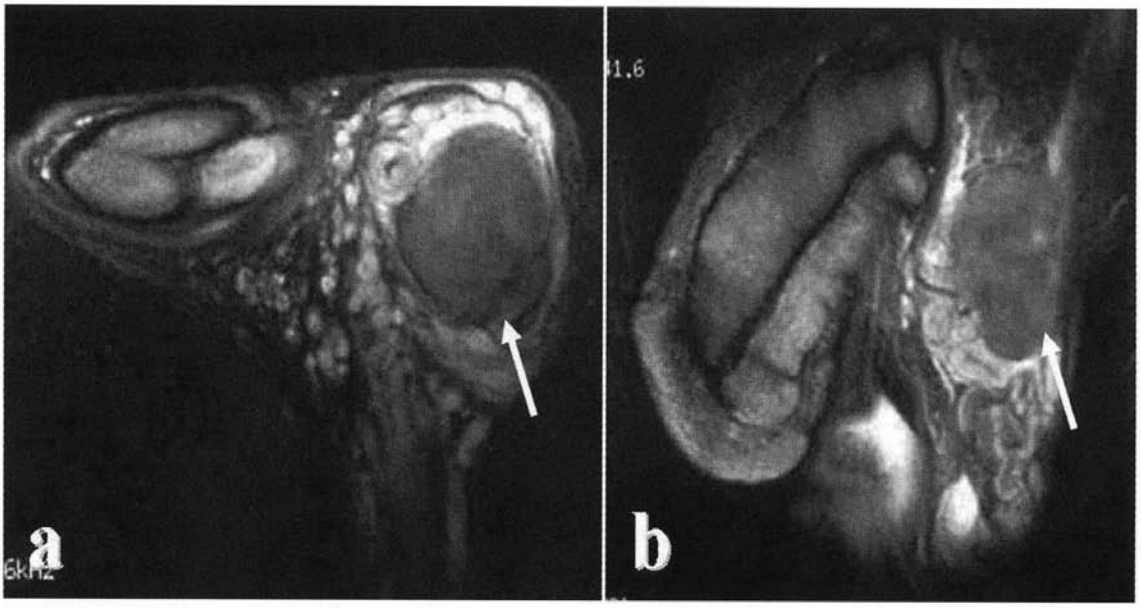

Figure 1. *Magnetic resonance image (T2-weighted image) of a smooth margined slightly low-intensity, 35×25 mm round mass (arrow), which involved the epididymis and spermatic cord. a: Axial image b: coronal image.*

LSC usually presents as a painless scrotal swelling, progressing in size slowly during a period ranging from months to years, as in the present case. Occasionally, a previously stable mass can rapidly increase in size. The average patient age at presentation is 55 years (range 16.5-85) with a slight right preponderance. Fewer than 6% of cases have a history of scrotal surgery or trauma (3). The clinical diagnosis in these conditions may be difficult, since the tumor can easily be mistaken for an inguinal hernia, hydrocele or spermatocele, as well as a tumor of the testis and epididymis. However, in the present case, a groin mass was palpable as a hard and fixed tumor. Therefore, the mass was suspected to be malignant.

Though liposarcomas have rarely been diagnosed preoperatively, ultrasonography, CT and MRI could provide useful information about the lipomatous nature of these masses.

The majority of spermatic cord tumors are benign (70-80%); lipoma is the most common. Malignant spermatic cord tumors are more frequently sarcomas (4). Rhabdomyosarcomas usually appear in young people and have a poor prognosis. Leiomyosarcomas, fibrosarcomas and liposarcomas are more commonly seen in older patients. LSC have been classified histologically into four categories, well-differentiated, dedifferentiated, myxoid and pleomorphic. Well-differentiated liposarcomas are further divided into adipocytic (lipoma-like), sclerosing liposarcoma, and into the two rare types of inflammatory and spindle cell liposarcoma. The sclerosing form is far more common in the retroperitoneum and spermatic cord than elsewhere (5).

Liposarcomas tend to spread primarily by local extension. When diagnosed or suspected preoperatively, radical orchiectomy with wide local excision is the recommended treatment for LSC. Adequate local resection provides the best chance of eradicating this disease. No therapeutic advantage has been attributed to superficial inguinal or retroperitoneal lymphadenectomy because liposarcomas tend to metastasize hematogenously rather than *via* the lymphatics.

Radiotherapy is controversial for local control of LSC. Liposarcomas are the most radiosensitive of all sarcomas and in some cases remission has been achieved with radiotherapy alone, although radiotherapy in eleven cases was reported to be associated with recurrence in five (3). In contrast, out of the 17 patients in some other studies treated with surgery and radiation, none had local recurrence (6-8). These retrospective reports provide no definitive evidence, but two prospective randomized trials on soft tissue sarcoma established that the addition of radiation to surgery substantially and significantly reduced the likelihood of local recurrence (9, 10). However, previously reported LSC series seemed not to be sufficiently large for a statistical analysis to demonstrate the necessity of additional radiotherapy. Our personal opinion is that radical surgical refinement with a negative margin is mandatory, whereas radiotherapy can be delayed if a close follow-up is performed. The role of chemotherapy for liposarcoma is not documented adequately.

In previous reports, the local recurrence rate after resection alone was 30-50% and local recurrence was the most common pattern of failure. Occasionally, local recurrence can be late. Thus, the customary 5-year landmark is not adequate to assess the therapeutic outcome. Regardless of initial therapy, the risk of local recurrence and subsequent increase in grade always necessitates long-term follow-up.

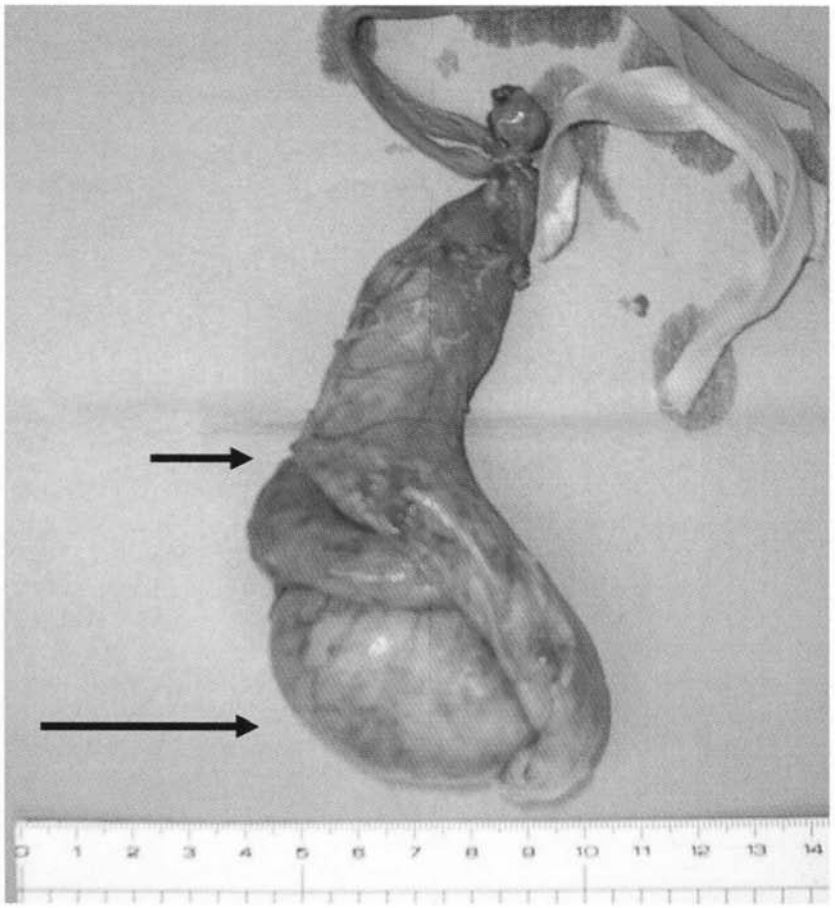

Figure 2. *Macroscopic appearance of the surgical specimen showing a capsulated mass (95×55 mm) composed mostly of adipose tissue infiltrating the left epididymis and spermatic structures (short arrow: spermatic cord tumor, long arrow: left testis).*

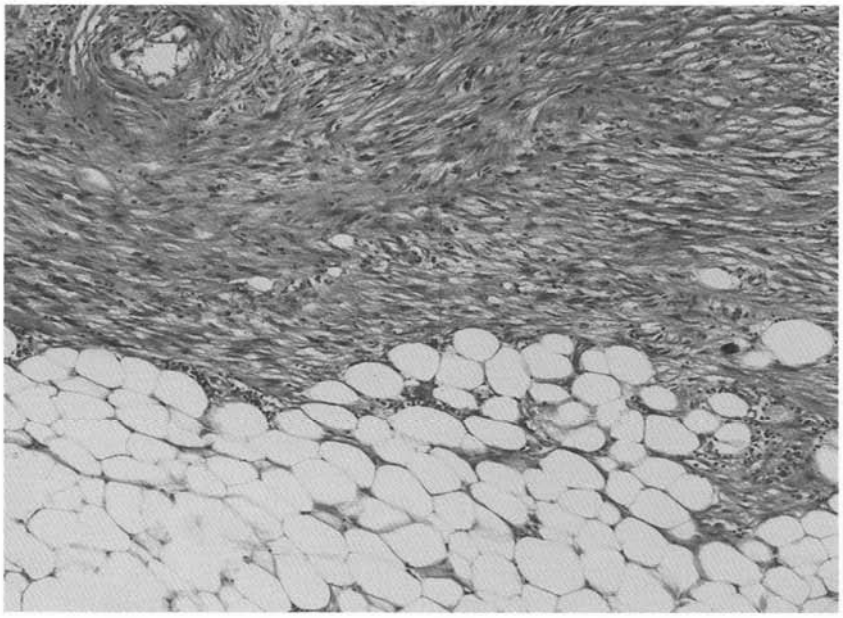

Figure 3. *Tumor showing a well-differentiated liposarcoma of fat cells and lipoblasts (lower half) and a dedifferentiated section with spindle cells having atypical highly multiplied nuclei like a myxofibrosarcoma (upper half) (×100).*

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