Clear Cell Sarcoma of Tendons and Aponeuroses

Juan Rodriguez-Martin, MD, Eduardo Ortiz-Cruz, MD, Julian Del Rio, MD, Teodoro Vivanco, MD, and Carlos Marti Lopez-Amor, MD

Ruber Clinic, Madrid, Spain

In this article, a case of clear cell sarcoma of the flexor hallucis longus in a 42-year-old woman is presented. The patient had previously been treated for suspected bursitis of the big toe. After extensive investigation, Lisfranc amputation was performed in order to achieve tumor-free margins. No adjuvant therapy was administered. At 5-year follow-up, there was no evidence of tumor recurrence or metastatic disease. The patient was functional in a modified shoe without the need for prosthesis. *Adv Orthop* 2011;**2**(4):156–60.

Originally described by Enzinger in 1965, clear cell sarcoma (CCS) is a high-grade soft tissue sarcoma seen in adolescents and young adults, with melanocytic differentiation typically involving tendons and aponeuroses [1]. In the past, CCS was called malignant melanoma of the soft parts, because it bears histological and immunohistochemical similarities to amelanotic melanoma and cellular blue nevus; however, it is a unique lesion distinct from cutaneous malignant melanoma [2,3]. CCS can be distinguished from melanoma by molecular biology, such as fluorescence *in situ* hybridization (FISH) and reverse transcriptase polymerase chain reaction (RT-PCR) [2–5]. The chromosomal translocation t(12;22)(q13;12) or the resultant fusion gene EWSR1-ATF1 is the hallmark of CCS [6–9].

In early reports, CCS was said to predominate in women, but several recent reports show an equal distribution between the sexes [2,3,10,11]. CCS occurs predominantly in young patients between 15 and 35 years of age [12], and the distal extremities are the main sites of involvement. CCS is more prevalent in white people than in African Americans and Asians [10].

The prognosis of CCS is poor, owing to a high percentage of regional lymph node metastases and distant metastases. An incidence of metastasis of 60–70% has been reported [13]. Typically, the tumor will recur locally approximately 2.5 years after treatment is initiated and will metastasize after 3–4 years. However, metastases have been seen up to 30 years after the initial diagnosis [14,15].

Wide excision or radical resection is the surgical treatment of choice for CCS according to the tumor margins [16–19], although other methods, including radiation, chemotherapy, arterial limb perfusion, and perilesional infusion of interferon α-2b (IFN-α-2b), have also resulted in apparent cure [20–22].

Beyond the soft tissues, CCS has also been described at other anatomical sites, including bone [23–30], pleura [31], kidney [32], penis [33], and gastrointestinal tract [34–42]. In this article, we report a case of CCS arising in the flexor hallucis longus tendon of a 42-year-old woman, and discuss the approach to diagnosis and treatment.

Case study

A 42-year-old woman with a diagnosis of CCS of the soft tissue in the first metatarsophalangeal joint was admitted to our clinic for definitive treatment. Her medical history was not contributory. One year before, she had presented with a soft tissue mass close to the first metatarsophalangeal joint, which increased until it was 4 cm and became painful. The presumptive diagnosis was bursitis of the great toe. She was treated with orthopaedic measures (e.g. shoe insoles and physiotherapy) and non-steroidal anti-inflammatory drugs, but experienced no improvement in the pain. Her doctor requested radiographs (**Figure 1**) and magnetic resonance imaging (MRI), which showed a soft tissue mass with no calcification arising in association with the flexor hallucis tendon, with hypointensity on T1-weighted images, hyperintensity on T2-weighted images, and gadolinium uptake (**Figure 2**). Fine-needle aspiration (FNA) was non-diagnostic and open excisional biopsy was carried out, followed by angular correction of the fifth metatarsal during the same surgery. The pathology report confirmed the presence of

Address for correspondence: Juan Rodriguez-Martin, Consulta Traumatología, Juan Bravo, 49 Dup, 6 planta, 28006, Madrid, Spain. Email: juanrodmar@yahoo.es

Figure 1. X-ray showing a soft tissue mass near the first metatarsophalangeal joint.

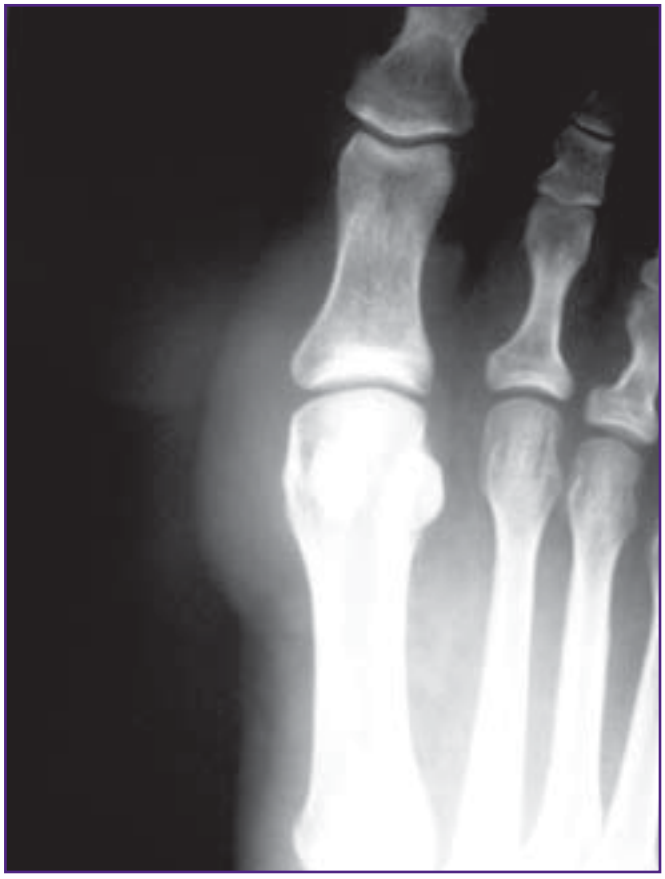
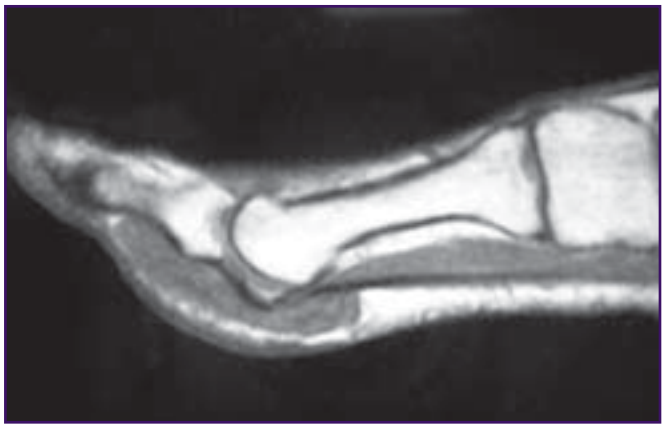
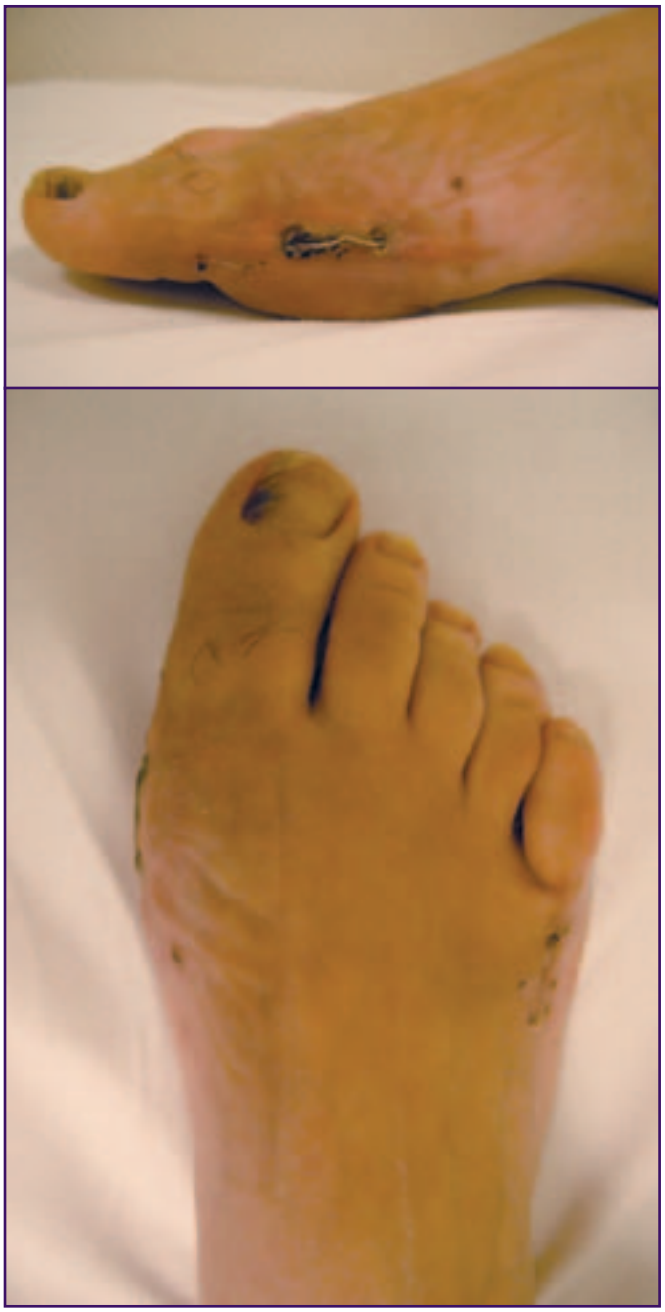


Figure 2. Magnetic resonance image showing a mass arising in association with the flexor hallucis longus tendon.



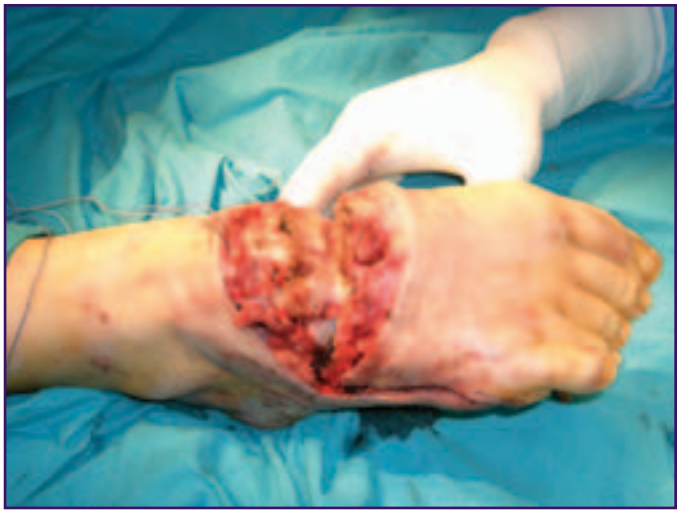
CCS with positive margins. The tumor size was 4.0×2.0×1.2 cm, with 10 mitotic cells per field, no necrosis, and malignant grade II/III. The tumor cells were pleomorphic and grew in sheets and fascicles. Immunohistochemistry showed neoplastic cells positive with HMB-45 and reactive to antibody against S100 protein. Detection of t(12;22)(q13;q12) was performed using FISH.

Figure 3. A: Surgical wound after excisional biopsy on the medial aspect of the first metatarsophalangeal joint. **B:** Surgical wound after angular correction on the dorsal aspect of the fifth metatarsophalangeal joint.



Upon physical examination at our clinic, 1 month after the biopsy, there was a surgical wound on the medial aspect of the first metatarsophalangeal joint (**Figure 3A**), without signs of infection or swelling, and another wound on the dorsal aspect of the fifth metatarsophalangeal joint (**Figure 3B**), also without any sign of infection. There were no other relevant signs or symptoms. Whole-body computed tomography showed no evidence of metastatic disease. Positron emission tomography and MRI demonstrated only postoperative changes.

Figure 4. A: Intraoperative photograph. Lisfranc amputation was performed in order to achieve tumor-free margins. B: Intraoperative photograph. The tibialis anterior and extensor common tendons were reattached proximally.



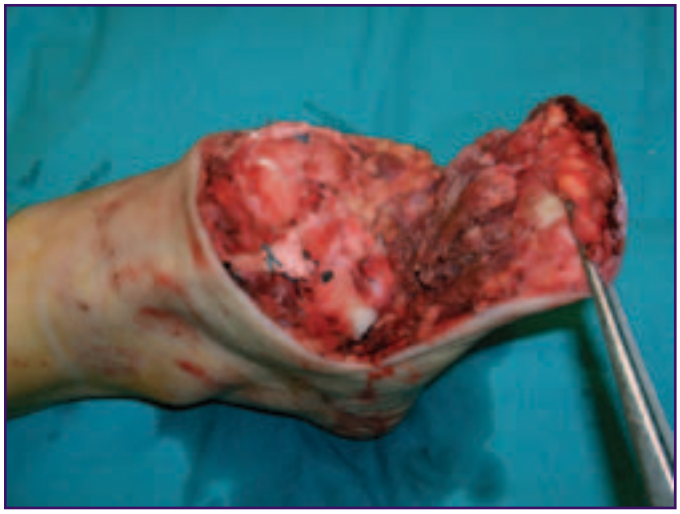
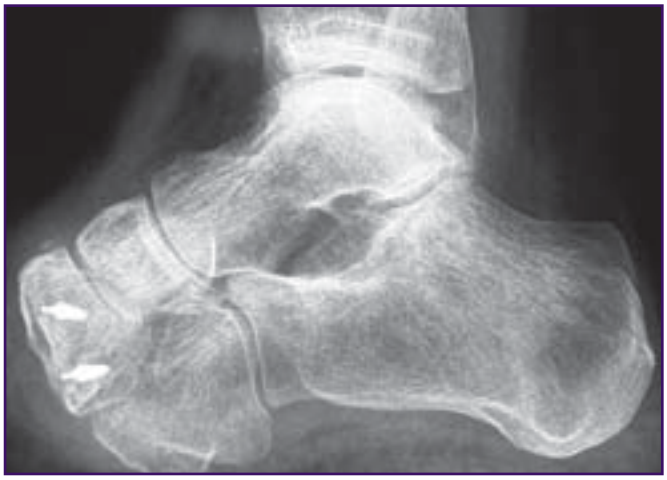


Figure 5. Postoperative radiograph. Lateral view.



After an interdisciplinary meeting between an oncologist, a radiologist, and orthopaedic oncology surgeons, the patient consented to undergo radical resection with Lisfranc amputation for definitive treatment (**Figure 4A**). Tibialis anterior and common extensor tendons were reattached to the second and third cuneiform bone remainders with two 3.5-mm suture anchors (Statack; Zimmer®, Warsaw, IN, USA; **Figure 4B)**. Intraoperative biopsy showed no tumor cell infiltration of the margins, and this was confirmed at definitive analysis of the resected tumor.

There were no intra- or postoperative complications (**Figure 5**). A well-padded posterior splint was placed to protect the amputation site and provide immobilization. The patient started partial weight-bearing at 4 weeks postoperatively, and total weight-bearing without crutches in a modified shoe at 6 weeks (**Figure 6**). At 5 years of follow-up, there was no evidence of recurrence or metastasis and the patient had no significant limitation of her daily activities.

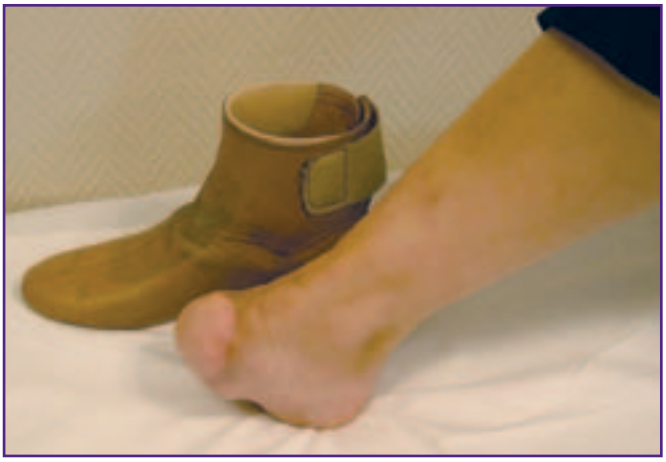
Discussion

CCS is a slow-growing malignant tumor of soft tissue. The diagnosis of CCS is often difficult because it is uncommon and has an unusual histopathology. On MRI, it appears as a well-circumscribed soft tissue mass, rarely invading adjacent bones, with variable signal intensity on T1-weighted and T2-weighted MRI. CCS should, however, be suspected when the lesion displays high signal on all sequences, including fat-saturation techniques [43,44], and also when calcifications, fluid-fluid levels, and marked hypointensities are absent within the mass [45].

Tumor response to the immunoperoxidase stains for S-100 and HMB-45 is helpful in diagnosis. It is important to differentiate between CCS and melanoma, because their prognosis and treatment differ substantially. However, this is not always possible on histological/immunohistochemical grounds alone [46]. In some situations, a genetic study is very helpful, because the t(12;22) translocation has never been reported in cutaneous melanoma [3,4,9]. Coindre et al. obtained positive results in 93% of CCS patients who were diagnosed by RT-PCR on paraffin-embedded tissues [9]. PCR-negative tumors can be explained by variant chromosomal translocations, such as t(2;22) with a EWS-CREB1 fusion, as reported recently [35]. Some PCR-negative tumors may also be melanoma with total regression of the primary or the superficial component. FISH using break-apart probes for EWS rearrangement is a good alternative to confirm the diagnosis. It is applicable for paraffin-embedded tissues and can be used overnight. However, it is not specific for CCS, because other tumors that show EWS rearrangement, such as Ewing sarcoma, desmoplastic round cell tumor, extraskeletal myxoid chondrosarcoma, and some myxoid/round cell liposarcomas, may show similar signals [9].

The prognosis for patients with CCS is poor, and they have a high propensity for regional lymph node and distant

Figure 6. Postoperative photograph. The patient was able to walk in a modified shoe without the use of prosthesis.



metastases. Recurrence and metastases have been reported up to 30 years after resection of the initial tumor. Lifelong surveillance is necessary for the early detection of recurrent disease. Metastases mainly occur in the regional lymph nodes and lungs, but can also affect brain, bone, or liver [10,47,48]. The use of sentinel lymph node biopsy has been proposed as an effective means of determining early occult regional metastases [49]. Poor prognostic indicators include a tumor size ≥5 cm, presence of metastases, and necrosis [11,17,50,51]. Recent large studies have added the depth of the tumor, sex, Tumor–Node–Metastasis stage, surgical margin, mitotic index, and histological grade to the list of prognostic factors [9,52].

Treatment by radical resection or amputation appears to have the most favorable results when a wide surgical margin is impossible to achieve or when the reconstruction is not functional [19]. Therefore, wide surgical resection has recently been proposed as the treatment of choice when the surgical oncology margin is adequate [53].

The beneficial effects of adjuvant chemotherapy and radiotherapy in CCS have not been fully evaluated [50]. Adjuvant radiotherapy has been used for improving local control, especially in the case of questionable resection margins [2,17,18,54]. Kawai et al. have argued that it should probably be assumed that patients with a tumor size >5 cm have micrometastases at the time of presentation, as these patients could benefit from adjuvant chemotherapy [52]. As CCS of tendons and aponeuroses shares many characteristics with malignant melanoma, investigation into the use of immunotherapy is warranted [11]. Steger reported a 17-month complete remission period in one patient treated with intralesional injection of IFN-α-2b [13].

In order to achieve tumor-free surgical margins, and owing to previous inadequate surgery of the first and fifth metatarsals, limb salvage surgery was not thought to be sufficient in our case; therefore, Lisfranc amputation was chosen. Excisional biopsy is not an appropriate option for diagnosis when malignancy is possible. In our patient, a tru-cut biopsy should have been performed to make the diagnosis instead of FNA, and excisional biopsy should not have been performed.

The Lisfranc amputation level is a viable option to preserve the length of the foot and offers the potential for retention of plantar load-bearing tissues, allowing patients to be functional in a modified shoe rather than a prosthesis [55]. When the decision is made to perform a Lisfranc amputation, one should consider the musculotendinous structures that are going to be encountered during this procedure. These structures are important to maintain the position and function of the foot. The tibialis posterior muscle provides inversion and plantar flexion of the foot. The insertion should be preserved because its main navicular insertion is not encountered during the procedure. The tibialis anterior tendon is a powerful dorsiflexor of the foot. If disturbed, it should be reattached to the proximal aspect of the medial cuneiform to preserve function. The peroneus brevis and tertius muscles are powerful evertors of the foot, and their insertions should be preserved if possible. Equinovarus deformity can result because of the loss of most of the dorsiflexors and the shortening of the foot. Ulceration of the distal stump can be a direct result of equinovarus deformity. Achilles tendon tenotomy or lengthening may be necessary to avoid this deformity [56].

Our case of CCS was misleading initially because of its location and clinical presentation. When a malignant tumor is possible, management including biopsy should be performed by an experienced multidisciplinary team in order to achieve good results [57].

Disclosure

The authors have no relevant financial interests to disclose.

References

1. Enzinger FM. Clear-cell sarcoma of tendons and aponeuroses. An analysis of 21 cases. *Cancer* 1965;**18**:1163–74.
2. Deenik W, Mooi WJ, Rutgers EJ et al. Clear cell sarcoma (malignant melanoma) of soft parts: a clinicopathologic study of 30 cases. *Cancer* 1999;**86**:969–75.
3. Patel RM, Downs-Kelly E, Weiss SW et al. Dual-color, break-apart fluorescence *in situ* hybridization for EWS gene rearrangement distinguishes clear cell sarcoma of soft tissue from malignant melanoma. *Mod Pathol* 2005;**18**:1585–90.
4. Graadt van Roggen JF, Mooi WJ, Hogendoorn PC. Clear cell sarcoma of tendons and aponeuroses (malignant melanoma of soft parts) and cutaneous melanoma: exploring the histogenetic relationship between these two clinicopathological entities. *J Pathol* 1998;**186**:3–7.

5. Langezaal SM, Graadt van Roggen JF, Cleton-Jansen AM et al. Malignant melanoma is genetically distinct from clear cell sarcoma of tendons and aponeurosis (malignant melanoma of soft parts). *Br J Cancer* 2001;**84**:535–8.
6. Antonescu CR, Tschernyavsky SJ, Woodruff JM et al. Molecular diagnosis of clear cell sarcoma: detection of EWS-ATF1 and MITF-M transcripts and histopathological and ultrastructural analysis of 12 cases. *J Mol Diagn* 2002;**4**:44–52.
7. Zucman J, Delattre O, Desmaze C et al. EWS and ATF-1 gene fusion induced by t(12;22) translocation in malignant melanoma of soft parts. *Nat Genet* 1993;**4**:341–5.
8. Hisaoka M, Ishida T, Kuo TT et al. Clear cell sarcoma of soft tissue: a clinicopathologic, immunohistochemical, and molecular analysis of 33 cases. *Am J Surg Pathol* 2008;**32**:452–60.
9. Coindre JM, Hostein I, Terrier P et al. Diagnosis of clear cell sarcoma by real-time reverse transcriptase-polymerase chain reaction analysis of paraffin embedded tissues: clinicopathologic and molecular analysis of 44 patients from the French sarcoma group. *Cancer* 2006;**107**:1055–64.
10. Finley JW, Hanypsiak B, McGrath B et al. Clear cell sarcoma: the Roswell Park experience. *J Surg Oncol* 2001;**77**:16–20.
11. Jacobs IA, Chang CK, Guzman G et al. Clear cell sarcoma: an institutional review. *Am Surg* 2004;**70**:300–3.
12. Chung EB, Enzinger FM. Malignant melanoma of soft parts. A reassessment of clear cell sarcoma. *Am J Surg Pathol* 1983;**7**:405–13.
13. Steger GG, Wrba F, Mader R et al. Complete remission of metastasised clear cell sarcoma of tendons and aponeuroses. *Eur J Cancer* 1991;**27**:254–6.
14. Tamburri SA, Boberg JS. Skeletally metastatic malignant melanoma of the foot. *J Foot Ankle Surg* 1994;**33**:368–72.
15. Wu KK. Clear cell sarcoma of the foot. *J Foot Surg* 1998;**27**:569–75.
16. Moseley HS. An evaluation of two methods of limb salvage in extremity soft-tissue sarcomas. *Arch Surg* 1992;**127**:1169–73.
17. Sara AS, Evans HL, Benjamin RS. Malignant melanoma of soft parts (clear cell sarcoma). A study of 17 cases, with emphasis on prognostic factors. *Cancer* 1990;**65**:367–74.
18. Eckardt JJ, Pritchard DJ, Soule EH. Clear cell sarcoma. A clinicopathologic study of 27 cases. *Cancer* 1983;**52**:1482–8.
19. Lucas DR, Nascimento AG, Sim FH. Clear cell sarcoma of soft tissues. Mayo Clinic experience with 35 cases. *Am J Surg Pathol* 1992;**16**:1197–204.
20. Lienard D, Ewalenko P, Delmotte JJ et al. High-dose recombinant tumor necrosis factor alpha in combination with interferon gamma and melphalan in isolation perfusion of the limbs for melanoma and sarcoma. *J Clin Oncol* 1992;**10**:52–60.
21. Lise M, Rossi CR, Alessio S et al. Multimodality treatment of extra-visceral soft tissue sarcomas M0: state of the art and trends. *Eur J Surg Oncol* 1995;**21**:125–35.
22. Radstone DJ, Revell PA, Mantell BS. Clear cell sarcoma of tendons and aponeuroses treated with bleomycin and vincristine. *Br J Radiol* 1979;**52**:238–41.
23. Brekke MK, Northcote K, Temple WE. Clear cell sarcoma in the first metatarsal. An unusual case. *J Am Podiatr Med Assoc* 1998;**88**:457–61.
24. Morishita S, Onomura T, Yamamoto S et al. Clear cell sarcoma of tendons and aponeuroses (malignant melanoma of soft parts) with unusual roentgenologic findings. Case report. *Clin Orthop Relat Res* 1987;**216**:276–9.
25. Raynor AC, Vargas-Cortes F, Alexander RW et al. Clear-cell sarcoma with melanin pigment: a possible soft-tissue variant of malignant melanoma. Case report. *J Bone Joint Surg Am* 1979;**61**:276–80.
26. Yokoyama R, Mukai K, Hirota T et al. Primary malignant melanoma (clear cell sarcoma) of bone: report of a case arising in the ulna. *Cancer* 1996;**77**:2471–5.
27. Hersekli MA, Ozkoc G, Bircan S et al. Primary clear cell sarcoma of rib. *Skeletal Radiol* 2005;**34**:167–70.
28. Gelczer RK, Wenger DE, Wold LE. Primary clear cell sarcoma of bone: a unique site of origin. *Skeletal Radiol* 1999;**28**:240–3.
29. Choi JH, Gu MJ, Kim MJ et al. Primary clear cell sarcoma of bone. *Skeletal Radiol* 2003;**32**:598–602.
30. Inaoka T, Takahashi K, Tandai S et al. Primary clear cell sarcoma (malignant melanoma) in the right radius. *Skeletal Radiol* 2003;**32**:594–7.
31. Bury T, Hermans G, Alexis-Agnant R et al. Clear cell sarcoma: an extremely rare cause of pleural disease. *Eur Respir J* 1997;**10**:2653–6.
32. Rubin BP, Fletcher JA, Renshaw AA. Clear cell sarcoma of soft parts: report of a case primary in the kidney with cytogenetic confirmation. *Am J Surg Pathol* 1999;**23**:589–94.
33. Saw D, Tse CH, Chan J et al. Clear cell sarcoma of the penis. *Hum Pathol* 1986;**17**:423–5.
34. Achten R, Debiec-Rychter M, De Wever I et al. An unusual case of clear cell sarcoma arising in the jejunum highlights the diagnostic value of molecular genetic techniques in establishing a correct diagnosis. *Histopathology* 2005;**46**:472–4.
35. Antonescu CR, Nafa K, Segal NH et al. EWS-CREB1: a recurrent variant fusion in clear cell sarcoma – association with gastrointestinal location and absence of melanocytic differentiation. *Clin Cancer Res* 2006;**12**:5356–62.
36. Covinsky M, Gong S, Rajaram V et al. EWS-ATF1 fusion transcripts in gastrointestinal tumors previously diagnosed as malignant melanoma. *Hum Pathol* 2005;**36**:74–81.
37. Friedrichs N, Testi MA, Moiraghi L et al. Clear cell sarcoma-like tumor with osteoclast-like giant cells in the small bowel: further evidence for a new tumor entity. *Int J Surg Pathol* 2005;**13**:313–8.
38. Fukuda T, Kakihara T, Baba K et al. Clear cell sarcoma arising in the transverse colon. *Pathol Int* 2000;**50**:412–6.
39. Pauwels P, Debiec-Rychter M, Sciot R et al. Clear cell sarcoma of the stomach. *Histopathology* 2002;**41**:526–30.
40. Taminelli L, Zaman K, Gengler C et al. Primary clear cell sarcoma of the ileum: an uncommon and misleading site. *Virchows Arch* 2005;**447**:772–7.
41. Venkataraman G, Quinn AM, Williams J et al. Clear cell sarcoma of the small bowel: a potential pitfall. Case report. *APMIS* 2005;**113**:716–9.
42. Ekfors TO, Kujari H, Isomaki M. Clear cell sarcoma of tendons and aponeuroses (malignant melanoma of soft parts) in the duodenum: the first visceral case. *Histopathology* 1993;**22**:255–9.
43. Hourani M, Khoury N, Mourany B et al. MR appearance of clear cell sarcoma of tendons and aponeuroses (malignant melanoma of soft parts): radiologic–pathologic correlation. *Skeletal Radiol* 2005;**34**:543–6.
44. De Beuckeleer LH, De Schepper AM, Vandevenne JE et al. MR imaging of clear cell sarcoma (malignant melanoma of the soft parts): a multicenter correlative MRI-pathology study of 21 cases and literature review. *Skeletal Radiol* 2000;**29**:187–95.
45. Isoda H, Kuroda M, Saitoh M et al. MR findings of clear cell sarcoma: two case reports. *Clin Imaging* 2003;**27**:229–32.
46. Creager AJ, Pitman MB, Geisinger KR. Cytologic features of clear cell sarcoma (malignant melanoma) of soft parts: a study of fine-needle aspirates and exfoliative specimens. *Am J Clin Pathol* 2002;**117**:217–24.
47. Hermann G, Klein MJ, Springfield DS et al. Clear cell sarcoma (malignant melanoma of soft parts): case report and review of the literature. *Can Assoc Radiol J* 2002;**53**:237–40.
48. Reichert B, Hoch J, Plotz W et al. Metastatic clear-cell sarcoma of the capitate. A case report. *J Bone Joint Surg Am* 2001;**83A**:1713–7.
49. Al-Refaie WB, Ali MW, Chu DZ et al. Clear cell sarcoma in the era of sentinel lymph node mapping. *J Surg Oncol* 2004;**87**:126–9.
50. Dim DC, Cooley LD, Miranda RN. Clear cell sarcoma of tendons and aponeuroses: a review. *Arch Pathol Lab Med* 2007;**131**:152–6.
51. Swanson PE, Wick MR. Clear cell sarcoma. An immunohistochemical analysis of six cases and comparison with other epithelioid neoplasms of soft tissue. *Arch Pathol Lab Med* 1989;**113**:55–60.
52. Kawai A, Hosono A, Nakayama R et al. Clear cell sarcoma of tendons and aponeuroses: a study of 75 patients. *Cancer* 2007;**109**:109–16.
53. Clark MA, Johnson MB, Thway K et al. Clear cell sarcoma (melanoma of soft parts): The Royal Marsden Hospital experience. *Eur J Surg Oncol* 2008;**34**:800–4.
54. Kuiper DR, Hoekstra HJ, Veth RP et al. The management of clear cell sarcoma. *Eur J Surg Oncol* 2003;**29**:568–70.
55. Yonclas PP, O'Donnell CJ. Prosthetic management of the partial foot amputee. *Clin Podiatr Med Surg* 2005;**22**:485–502.
56. DeCotiis MA. Lisfranc and Chopart amputations. *Clin Podiatr Med Surg* 2005;**22**:385–93.
57. Ortiz Cruz EJ, García Rey E, Dhimes Tejada P et al. Assessment of tumoural lesions of the foot and ankle. *Rev Pie y Tobillo* 2005;**29**:12–31.