Cancer Association of South Africa (CANSA)

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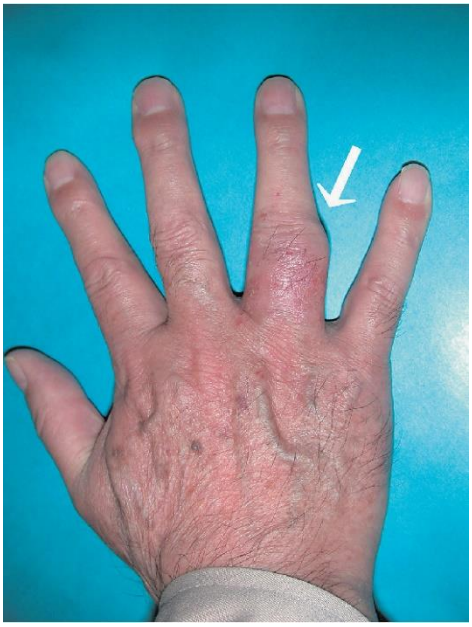
Fact Sheet on Extraskeletal Myxoid Chondrosarcoma

Introduction

Chondrosarcoma is a rare type of cancer that usually begins in the bones, but can sometimes occur in the soft tissue near bones. The most common locations for chondrosarcoma tumours are in the pelvis, hip and shoulder. More rarely, the base of the skull is affected.



[Picture Credit: Extraskeletal Myxoid Chondrosarcoma Picture]

The defining characteristic of a chondrosarcoma is that its cells produce cartilage. Some types of chondrosarcomas grow slowly and, provided they are removed completely, have a low risk of spreading to other organs and bones. Others grow rapidly and have a high risk of metastasis.

Surgical removal of the tumour is the mainstay of chondrosarcoma treatment. Radiation and chemotherapy are rarely helpful in the treatment of chondrosarcoma.

Extraskeletal Myxoid Chondrosarcoma (EMC)

Extraskeletal Myxoid Chondrosarcoma (EMC) is a rare malignant mesenchymal neoplasm of uncertain differentiation characterized by rearrangements of the NR4A3 gene. EMCS is an intermediate-grade tumour that represents less than 3% of all soft tissue sarcomas.

EMC usually affects middle-aged or older adults, and is rare in children and adolescents – it is found most often in adults males around the age of 50 and arise in the deep tissues of the proximal extremities and limb girdles. It usually occurs in the thigh, knee, buttock, or trunk (chest and abdomen). The tumour may grow large and spread to nearby tissue or to other parts of the body, including the lymph nodes and lungs.

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EMC is characterized by indolent growth rate but strong tendency to local recurrence and metastatic spread. No specific systemic treatment has yet been approved by the US Food and Drug Administration (FDA) for this disease and surgery has been traditionally the only potentially curative strategy.

Khader, A.I., Nsour, E., Al-Zubi, R.B. & Al Maadat, H.M.D. 2019.
RATIONALE: Extraskeletal myxoid chondrosarcoma is a slow-growing soft tissue tumor of adults with a propensity for local recurrence and eventual metastasis. Only 17 pediatric and adolescent cases have been reported.
PATIENT CONCERNS: Here we present an 11-year-old boy with a 3-year history of a slowly growing painless left leg mass. Magnetic resonance imaging of the lesion revealed a subfascial well-circumscribed lesion with intramuscular extension in the medial gastrocnemius muscle of the left leg.
DIAGNOSES: He underwent wide local excision of the mass and the histomorphological and immunohistochemical findings were consistent with extraskeletal myxoid chondrosarcoma.
INTERVENTIONS: Possible radiotherapy was the further management plan.
OUTCOMES: He was in good condition with no evidence of recurrence at 6 months postsurgery.
LESSONS: Although pediatric cases of extraskeletal myxoid chondrosarcoma were reported to be aggressive, the tumor in this case demonstrated indolent behavior. Furthermore, the tumor in this case showed primitive round cell foci which adds to a previous study that especially reported this morphology in pediatric cases.

Paoluzzi, L. & Ghesani, M. 2018.
BACKGROUND: Extraskeletal myxoid chondrosarcoma (EMC) is a rare malignant mesenchymal neoplasm of uncertain differentiation characterized by rearrangements of the NR4A3 gene. EMC often affects adults around the age of 50 and arise in the deep tissues of the proximal extremities and limb girdles. EMC is characterized by indolent growth rate but strong tendency to local recurrence and metastatic spread. No systemic treatment is specifically approved by the FDA for this disease and surgery has been traditionally the only potentially curative strategy.
CASE PRESENTATION: A 41-year-old Caucasian woman originally presented with a 14.8 cm left thigh mass. She was managed with wide local resection but after 2 years she developed recurrent disease in the pelvis and in the lungs; the lung involvement was characterized by innumerable nodules without any significant respiratory symptoms. After failing three clinical trials, she experienced prolonged disease control while on treatment with the tyrosine kinase inhibitor (TKI) pazopanib and radiation therapy delivered to the pelvic lesion. Dose reduction of pazopanib due to severe diarrhea was followed by rapid disease progression in the pelvis requiring vascular stenting; increase in tumor growth after discontinuation of a TKI has been described in other malignancies and is a possibility in this specific patient.
CONCLUSION: While surgical management of EMC with or without radiation therapy is still the preferable approach when feasible, small series support the use of tyrosine kinase inhibitors and possible new immunotherapies in selected patients. Basket trials focusing on diseases with unique genomic features such as EMC will hopefully provide a better understanding of new options for care.

Elsayed, A.G., Al-Qawasmi, L., Katz, H. & Lebowicz, Y. 2018.
"Extraskeletal myxoid chondrosarcoma (EMC) is a rare soft tissue sarcoma with an indolent course and poor response to systemic treatment. We present a case of a 53-year-old male who presented with right gluteal extraskeletal myxoid chondrosarcoma. He was treated with wide local excision after receiving 50 Gray of neoadjuvant radiation therapy. Three years later he was found to have a left lower lobe lung nodule that was slowly increasing in size. He underwent a left lower lobectomy and the nodule was confirmed to be

consistent with the patient's history of EMC. One year later, lung imaging showed multiple small nodules bilaterally consistent with metastatic disease. The patient opted for watchful waiting approach. Routine follow-up imaging for four years shows a very slow progression of his disease burden. He continues to be asymptomatic. This case demonstrates the natural course of EMC and argues in favor of the watchful waiting approach in treating this disease."

Incidence of Extraskeletal Chondrosarcoma (EMC)

The South African National Cancer Registry does not provide any information regarding Extraskeletal Chondrosarcoma.

Signs and Symptoms of Extraskeletal Chondrosarcoma (EMC)

Swollen localised tumours, found mostly in the pelvis, hip and shoulder. More rarely, the base of the skull is affected.

Diagnosis of Extraskeletal Chondrosarcoma (EMC)

Cases of Extraskeletal Chondrosarcoma are diagnosed mainly on clinical presentation and genetic studies following a biopsy in the form of fine-needle aspiration.

Wilson, J.T., Pitts, C., Hess, M., Phillips, S.G., Siegal, G.P. & Johnson, M.D. 2019.

CASE: Extraskeletal myxoid chondrosarcoma (EMC) is a rare soft tissue malignancy that very seldomly presents in the foot or ankle and as a result is not commonly in the differential of patients presenting with foot pain. We cite a case of EMC presenting in the atypical location of the midfoot. Because of its location and similarities, this tumor was initially misdiagnosed and mistreated by multiple medical providers as midfoot Charcot arthropathy.

CONCLUSIONS: Neoplastic etiologies, including EMC, should remain in the differential for atypical, refractory foot pain that presents in a manner similar to Charcot foot.

Santos, F., Martins, C. & Lemos, M.M. 2018.

BACKGROUND: Extraskeletal myxoid chondrosarcoma (EMC) is a tumor of uncertain differentiation. Few data are available regarding its cytomorphological features in fine-needle aspiration (FNA). Specific cytogenetic alterations involving the NR4A3 gene are found in EMC and can be identified in FNA samples.

METHODS: We retrospectively reviewed 14 FNAs performed in 11 patients with an EMC; 10 FNAs were performed preoperatively on primary tumors; 2 were performed on recurrences and 2 were performed on metastasis. Cytological features were compared with histological findings. Immunohistochemistry (IHC) and molecular studies were performed both in FNA and histological specimens.

RESULTS: A preoperative cytological diagnosis of EMC was rendered in eight FNAs performed in newly diagnosed tumors and in recurrent/metastatic cases. A descriptive diagnosis of a myxoid neoplasm was made in the remaining two cases. Smears were moderately hypercellular, composed of plasmocytoid to fusiform cells, with scant, pale cytoplasm, bland nuclei and inconspicuous nucleoli, dispersed as cords, strands and occasionally with a lace-like pattern, in an abundant chondromyxoid matrix. IHC performed showed focal positivity for S100 and NSE. Fluorescence in situ hybridization technique performed in three FNA specimens showed EWSR1 gene rearrangements in all, concomitant with NR4A3 gene rearrangement

in one case. Histological specimens showed typical features of EMC and NR4A3 gene rearrangements were found in all cases tested.
CONCLUSION: FNA cytology is a reliable method to perform a preoperative diagnosis of EMC regarding its cytomorphological and molecular features. Main differential diagnoses include myoepithelial tumors of soft tissue, myxoid liposarcoma and myxofibrosarcoma. Ancillary studies are helpful when coupled with cytomorphology evaluation.

Brenca, M., Stacchiotti, S., Fassetta, K., Sbaraglia, M., Janjusevic, M., Racanelli, D., Polano, M., Rossi, S., Brich, S., Dagrada, G.P., Collini, P., Colombo, C., Gronchi, A., Astolfi, A., Indio, V., Pantaleo, M.A., Picci, P., Casali, P.G., Dei Tos, A.P., Pilotti, S. & Maestro, R. 2019.
"Extraskeletal myxoid chondrosarcoma (EMC) is a rare sarcoma histotype with uncertain differentiation. EMC is hallmarked by the rearrangement of the NR4A3 gene, which in most cases fuses with EWSR1 or TAF15. TAF15-translocated EMC seem to feature a more aggressive course compared to EWSR1-positive EMCs, but whether the type of NR4A3 chimera impinges upon EMC biology is still largely undefined. To gain insights on this issue, a series of EMC samples (7 EWSR1-NR4A3 and 5 TAF15-NR4A3) were transcriptionally profiled. Our study unveiled that the two EMC variants display a distinct transcriptional profile and that the axon guidance pathway is a major discriminant. In particular, class 4-6 semaphorins and axonal guidance cues endowed with pro-tumorigenic activity were more expressed in TAF15-NR4A3 tumors; vice versa, class 3 semaphorins, considered to convey growth inhibitory signals, were more abundant in EWSR1-NR4A3 EMC. Intriguingly, the dichotomy in axon guidance signaling observed in the two tumor variants was recapitulated in in vitro cell models engineered to ectopically express EWSR1-NR4A3 or TAF15-NR4A3. Moreover, TAF15-NR4A3 cells displayed a more pronounced tumorigenic potential, as assessed by anchorage-independent growth. Overall, our results indicate that the type of NR4A3 chimera dictates an axon guidance switch and impacts on tumor cell biology. These findings may provide a framework for interpretation of the different clinical-pathological features of the two EMC variants and lay down the bases for the development of novel patient stratification criteria and therapeutic approaches. © 2019 The Authors. The Journal of Pathology published by John Wiley & Sons Ltd on behalf of Pathological Society of Great Britain and Ireland."

Treatment of Extraskeletal Chondrosarcoma (EMC)
Treatment of Extraskeletal Chondrosarcoma is mainly surgical excision, with possible adjuvant chemotherapy. No specific systemic treatment has yet been approved by the US Food and Drug Administration (FDA) for this disease

Chow, W., Frankel, P., Ruel, C., Araujo, D.M., Milhem, M., Okuno, S., Hartner, L., Undevia, S. & Staddon, A. 2020.
BACKGROUND: This single-arm, multicenter, phase 2 study evaluated the safety and antitumor activity of pazopanib in patients with unresectable or metastatic conventional chondrosarcoma.
METHODS: Eligible patients had conventional chondrosarcoma of any grade with measurable tumors that were unresectable or metastatic. Patients with mesenchymal, dedifferentiated, and extraskeletal myxoid chondrosarcoma subtypes and patients who received prior tyrosine kinase inhibitor therapy were excluded. Pazopanib at 800 mg once daily was administered for 28-day cycles. Tumor responses were evaluated by local radiology assessments every 2 cycles. The primary endpoint was the disease control rate (DCR) at week 16 (4 cycles).
RESULTS: Forty-seven patients were enrolled. The DCR at 16 weeks was 43% (95% confidence interval [CI], 28%-58%), which was superior to the null hypothesis rate of 30%, but the 2-sided P value (exact test) was

.09 (1-sided P = .045). One patient had a partial response. The median overall survival was 17.6 months (95% CI, 11.3-35.0 months), and the median progression-free survival was 7.9 months (95% CI, 3.7-12.6 months). Grade 3 or higher adverse events were infrequent; hypertension (26%) and elevated alanine aminotransferase (9%) were most common.
CONCLUSIONS: This study provides evidence of positive drug activity for pazopanib in conventional chondrosarcoma.

Stacchiotti, S., Ferrari, S., Redondo, A., Hindi, N., Palmerini, E., Vaz Salgado, M.A., Frezza, A.M., Casali, P.G., Gutierrez, A., Lopez-Pousa, A., Grignani, G., Italiano, A., LeCesne, A., Dumont, S., Blay, J.Y., Penel, N., Bernabeu, D., de Alava, E., Karanian, M., Morosi, C., Brich, S., Dagrada, G.P., Vallacchi, V., Castelli, C., Brenca, M., Racanelli, D., Maestro, R., Collini, P., Cruz, J. & Martin-Broto, J. 2019.
BACKGROUND: Extraskeletal myxoid chondrosarcoma is a rare sarcoma with low sensitivity to cytotoxic chemotherapy. Retrospective evidence suggests that antiangiogenic drugs could be a treatment option. We aimed to investigate the activity of pazopanib, an antiangiogenic drug, in patients with advanced extraskeletal myxoid chondrosarcoma.
METHODS: In this single-arm, open-label phase 2 trial, three parallel independent cohorts of different histotypes of advanced sarcomas were recruited (extraskeletal myxoid chondrosarcoma, typical solitary fibrous tumour, and malignant-dedifferentiated solitary fibrous tumour). In each cohort, patients received pazopanib. In this Article, we report the results of the cohort of patients with advanced extraskeletal myxoid chondrosarcoma. Separate reporting of the three cohorts was prespecified in the study protocol. In this cohort, adult patients (aged ≥18 years) with a diagnosis of NR4A3-translocated, metastatic, or unresectable extraskeletal myxoid chondrosarcoma, who had Response Evaluation Criteria in Solid Tumors (RECIST) progression in the previous 6 months, and had an Eastern Cooperative Oncology Group performance status of 0-2, were enrolled at 11 study sites of the Spanish, Italian, and French sarcoma groups. Patients received oral pazopanib (800 mg/day) continuously, until disease progression, unacceptable toxicity, death, non-compliance, patient refusal, or investigator's decision. The primary endpoint was the proportion of patients achieving an objective response according to RECIST 1·1 in the modified intention-to-treat population (patients who provided consent and had a central molecularly confirmed diagnosis of extraskeletal myxoid chondrosarcoma). The safety analysis included all patients who received at least one dose of pazopanib. This study is registered with ClinicalTrials.gov, number NCT02066285.
FINDINGS: Between June 24, 2014, and Jan 17, 2017, 26 patients entered the study and started pazopanib. Of these, 23 met the eligibility criteria for the modified intention-to-treat analysis. Median follow-up was 27 months (IQR 18-30). 22 patients (one patient died before the primary analysis) were evaluable for the primary endpoint: four (18% [95% CI 1-36]) had a RECIST objective response. No deaths or grade 4 adverse events occurred. The most frequent grade 3 adverse events were hypertension (nine [35%] of 26 patients), increased concentration of alanine aminotransferase (six [23%]), and increased aspartate aminotransferase (five [19%]).
INTERPRETATION: Pazopanib had clinically meaningful antitumour activity in patients with progressive and advanced extraskeletal myxoid chondrosarcoma, and could be considered a suitable option after failure to respond to first-line anthracycline-based chemotherapy in these patients.
FUNDING: Spanish Group for Research on Sarcomas, Italian Sarcoma Group, French Sarcoma Group, GlaxoSmithKline, and Novartis.

About Clinical Trials
Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The *South African National Clinical Trials Register* provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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Extraskeletal Myxoid Chondrosarcoma Picture
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