Cancer Association of South Africa (CANSA)

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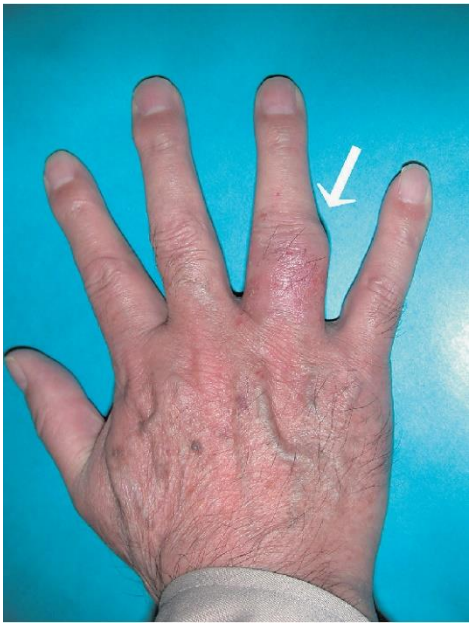
Fact Sheet on Extraskeletal Myxoid Chondrosarcoma

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.

Claxton, M.R., Reynolds, G., Wenger, D.E., Rose, P.S. & Houdek, M.T. 2020.
Background: Extraskeletal myxoid chondrosarcoma (ESMC) is a rare type of soft-tissue sarcoma with limited series reporting outcome of treatment. Currently there is limited data on the incidence and impact on patient outcome in those with metastatic disease to lymph nodes in ESMC.
Methods: Thirty (21 males, 9 females) patients, mean age 50 ± 16 years, with ESMC were reviewed. The tumors were most commonly located in the lower extremity (n = 23, 77%) and the mean tumor size and volume were 9 ± 5 cm and 490 ± 833 cm^3 . Mean follow up was 7 ± 4 years.
Results: Six (20%) patients either presented (n = 3, 10%) or developed (n = 3, 10%) lymph node metastatic disease. When comparing patients without, with lymph node metastasis and metastasis elsewhere, patients with lymph nodes metastasis had worse survival than those without metastasis, however better 10-year disease specific survival than those with metastasis elsewhere (100% vs 62% vs 0%; P < .001).
Conclusion: There is a high incidence of lymph node metastatic disease in patients with ESMC. Although survival in these patients is worse compared to those without metastasis, their survival is better than those with metastasis elsewhere. Due to the high incidence of lymph node metastatic disease, preoperative staging of the lymph node should be considered.

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.

Tumour Grade and Tumour Stage
Tumour grade and stage are terms used to describe the severity of a tumour, while tumour grade describes the appearance of cancerous cells in the tissue by examining them under a microscope.

Tumour stage encompasses:

- The location of the tumour.
- The size and/or extent of the original tumour.
- Whether cancer cells have spread to lymph nodes or anywhere else in the body.
- The number of tumours present.

Doctors use tumour grade, cancer stage, and a patient's age and general health to decide the course of treatment for the patient and determine prognosis. Prognosis describes all factors including the disease course, cure rate, chances of survival, and risk of recurrence of cancer.

What are the cancer stages?

Different systems of cancer staging are used to describe the types of cancer. Below is a common method in which stages are ranged from 0 to IV.

- Stage 0: The tumour is confined to its place of origin (in situ) and has not spread to nearby tissue.
- Stage I: The tumour is located only in the original organ, is small, and has not spread.
- Stage II: The size of the tumour is large but has not spread.
- Stage III: The tumour has become larger and may have spread to surrounding tissues and/or lymph nodes.
- Stage IV: The tumour has spread to other distant organs of the body, which is known as the metastasis stage.

TNM staging

Another common staging method used for cancer is the TNM system, which stands for tumour, node (which means spread of the tumour to lymph nodes), and metastasis. When a patient's cancer is staged using the TNM system, a number will be present along with the letter. This number signifies the extent of the disease in each category - tumour, node, and metastases.

Another system of cancer staging divides cancer into five stages, which include:

- In situ: Abnormal cells are present but have not spread to nearby tissue.
- Localized: Cancer is located only in the original organ and shows no sign of its spread.
- Regional: Cancer has spread to nearby lymph nodes, tissues, or organs.
- Distant: Cancer has spread to distant parts of the body.
- Unknown: The stage cannot be figured out due to a lack of enough information.

What are the cancer grades?

Cancer grades are based on examination of the suspected tissue sample under a microscope. This involves surgically removing a piece of the suspected cancerous tissue and sending it to the lab for analysis. The entire procedure is known as a biopsy.

A doctor who specializes in diagnostic tests (pathologist) examines the cells of the tissue and determines whether they are harmless (benign or noncancerous) or harmful (malignant or cancerous). They describe the microscopic appearance of the cells and assign a numerical "grade" to most cancers.
Generally, a lower grade indicates slow-growing cancer and a higher grade indicates fast-growing cancer.

The most commonly used grading system is as follows:

- Grade I: Cancer cells that look like normal cells but are not growing rapidly.
- Grade II: Cancer cells that don't look like normal cells with their growth being faster than normal cells.
- Grade III: Cancer cells that look abnormal and have the potential to grow rapidly or spread more aggressively.

Sometimes, the following system can be used:

- GX: Grade cannot be assessed (undetermined grade)
- G1: Well-differentiated (low grade)
- G2: Moderately differentiated (intermediate grade)
- G3: Poorly differentiated (high grade)
- G4: Undifferentiated (high grade)

Incidence of Extraskeletal Chondrosarcoma (EMC)
The South African National Cancer Registry (2017) +600does 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.

Wakely, P.E. Jnr. 2020.
Introduction: Advances in the genetics of soft tissue neoplasia have allowed for the diagnostic recognition of specific tumor types from small biopsy specimens, including those procured using the fine needle aspiration (FNA) biopsy technique. Extraskeletal myxoid chondrosarcoma (EMC) is a malignant mesenchymal neoplasm characterized by NR4A3 and, less specifically, by EWSR1 gene rearrangements. A series of EMC cytologic specimens was examined to demonstrate the diagnostic value of incorporating fluorescence in situ hybridization (FISH) testing in cytologic cases of suspected EMC.
Materials and methods: A search was made of our cytopathology and surgical pathology databases for cases diagnosed as EMC. FNA biopsy cytology, exfoliative cytology, imprint cytology, and FISH analysis were performed and examined using standard techniques.
Results: A total of 16 cases of EMC were retrieved from 15 patients (male/female ratio, 2.8:1; mean age, 62 years). Of the 15 patients, 10 were new patients with primary tumors, 2 had locally recurrent tumors, and 4 had metastases. The sites included the extremities in 10 cases, the trunk in 4, serous effusion in 1, and a mediastinal lymph node in 1 case. The specific cytologic diagnoses were EMC (14 cases; 88%), suspicious for EMC (n = 1), and malignant cells (n = 1). All cases for which FISH testing was successfully used were specifically recognized as EMC. Aspirates and imprint smears consisted of uniformly rounded cells set in an opaque myxoid/chondromyxoid stroma (less abundant and more diaphanous in the effusion sample), sometimes arranged in short anastomosing cords. FNA of 1 case of an EMC cellular variant mimicked a malignant small rounded cell tumor.
Conclusion: EMC can be added to the growing list of soft tissue neoplasms that are specifically recognizable using cytopathology, coupled with judicious application of ancillary molecular testing.

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.

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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Tumour Grade and Tumour Stage
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