

Paediatric Clear Cell Sarcoma of Scalp Masquerading as Benign Sebaceous Cyst: A Diagnostic Dilemma

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ABSTRACT

Clear Cell Sarcoma of Soft Tissue (CCSST) is a rare and aggressive tumour comprising 1% of all soft tissue sarcomas. They tend to recur locally and have a high predilection for regional, as well as, distant metastases. These tumours usually occur in a young age group; however, their presentation in childhood is extremely rare. They are also known as Malignant Melanoma (MM) of soft parts due to similar histological and Immunohistochemical (IHC) features with MM. Distinguishing between them is very difficult morphologically. Both exhibit high lymph node metastases and positive staining for S-100 protein, Melanoma antigen (Melan-A) and Human Melanoma Black-45 (HMB-45). Here, the authors reported an unusual case of an 11-year-old male child who presented with a slowly progressing scalp swelling that was misdiagnosed as a sebaceous cyst radiologically and on Fine Needle Aspiration Cytology (FNAC), which later turned out to be CCSST on histopathology. Unfortunately, the patient was lost to follow-up, but later presented with multiple cutaneous swellings, emphasising the tumour's aggressive nature. The index case is being reported as an exception to its age of occurrence and unusual presentation that posed a diagnostic dilemma, leading to a delay in treatment. The treatment for CCSST involves wide surgical resection with negative margins, and adjuvant therapy may be considered based on resection outcomes. In conclusion, the present case underscores the diagnostic challenges posed by CCSST, particularly when it occurs in atypical age groups and locations. Timely recognition and differentiation from similar entities, such as MM, are crucial for appropriate management and improved outcomes.

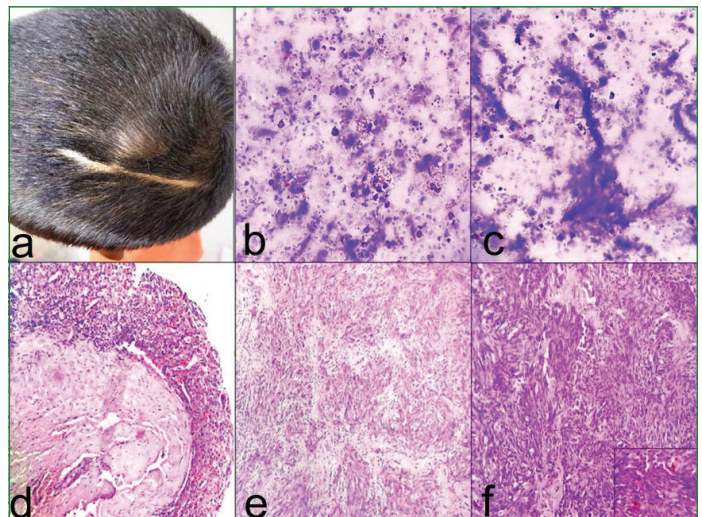
Keywords: Childhood malignancy, Ewing sarcoma breakpoint region 1, Malignant melanoma

CASE REPORT

An 11-year-old male child presented to the Department of Ear, Nose and Throat (ENT) with a complaint of a scalp swelling for one year. The swelling was gradually progressive and painless. There was no history of loss of appetite, weight loss, or fever. His past history and family history were also insignificant. On examination, the swelling was soft to firm, cystic, non mobile, non tender, located on the left parietal region and measured approximately 3×3 cm in size [Table/Fig-1a]. Pallor was present on physical examination, and the haematological profile suggested microcytic hypochromic anaemia, likely due to poor nutritional status. Other biochemical parameters (kidney function test and liver function test) were within normal limits. A Computed Tomography (CT) scan of the swelling revealed a hypodense cystic lesion in the left high parietal region in the scalp measuring 31×17 mm in size, suggestive of a sebaceous cyst. He was advised to undergo a cytological examination. FNAC was attempted, and 3 mL of brownish fluid was aspirated. The swelling regressed in size after aspiration. Smears prepared were paucicellular and showed predominantly macrophages laden with pigment (haemosiderin) along with degenerated debris (keratin material) in a haemorrhagic and proteinaceous background [Table/Fig-1b,c]. The FNAC findings suggested a benign cystic lesion. Excision was requested for confirmation.

The excised cyst was sent for Histopathological Examination (HPE) by the Department of Surgery with a clinical diagnosis of a sebaceous cyst in the left parietal region (suggested on radiology). Grossly, multiple irregular, grey-white, cystic, firm tissue bits measuring 3×2×2 cm in total were received. On histopathology, sections revealed a cellular tumour comprising a dual morphology of cells, with spindle cells forming short intersecting fascicles and whorls around small-caliber blood vessels, large with plump ovoid to elongated nuclei showing moderate pleomorphism, inconspicuous nucleoli and a moderate amount of eosinophilic cytoplasm. Focal cytoplasmic vacuolisation was noted in spindle

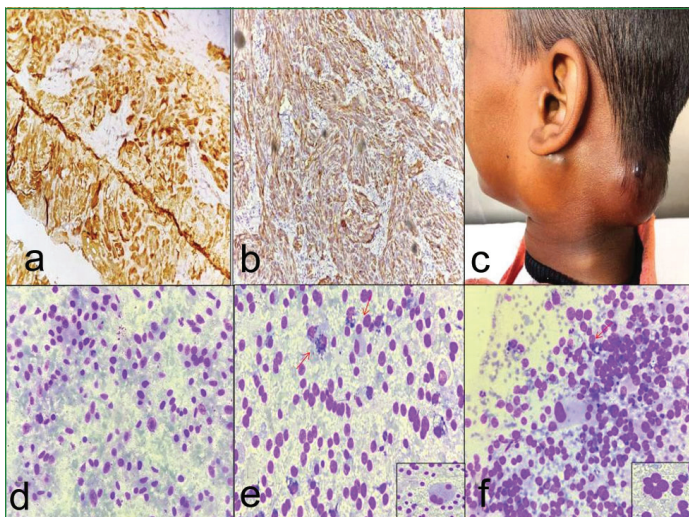
cells. Interspersed among these fascicles were multinucleated cells, foamy macrophages and mononuclear inflammatory infiltrates. Pigment-studded macrophages were observed lining the cyst wall and interspersed among the cells [Table/Fig-1d,e]. Another population of cells consisted of round to ovoid cells, with some showing a plasmacytoid morphology, vesicular chromatin, prominent nucleoli and scant to a moderate amount of eosinophilic cytoplasm. Clear cell change was also evident [Table/Fig-1f]. Mitotic



[Table/Fig-1]: a) Clinical picture of child with scalp swelling; b) FNAC smear of scalp swelling displaying numerous macrophages laden with pigment (haemosiderin) along with degenerated debris (MGG; 200x); c) FNAC smear of scalp swelling displaying numerous macrophages laden with pigment along with degenerated in a haemorrhagic and proteinaceous background (MGG; 200x); d) HPE of scalp swelling displaying a cyst wall studded with macrophages and inflammatory cells and red blood cells (H&E; 200x); e) HPE of scalp swelling displaying cellular tumour comprising of dual morphology of cells, comprising of spindle cells in short intersecting fascicles and round to ovoid cells with few of cells bearing plasmacytoid morphology (H&E; 200x); f) HPE of scalp swelling displaying cellular tumour with spindle cells in fascicular pattern displaying hyperchromatic nuclei. Inset showing pigment-laden macrophage (H&E; 200x).
MGG: May-Grünwald-Giemsa

activity was brisk with atypical mitosis. A provisional diagnosis of MM and clear cell sarcoma was made. IHC for S-100, HMB-45 and Melan-A was performed to confirm the diagnosis [Table/Fig-2a,b]. All three markers were positive, leading to a final diagnosis of clear cell sarcoma of soft tissue.

The patient failed to collect the histopathology report and was lost to follow-up due to erroneous contact details. Eight months later, he presented to the Surgery Outpatient Department (OPD) with multiple cutaneous swellings on the head and neck. On examination, three swellings were noted on the left occipital, cervical and suprascapular regions, ipsilaterally, measuring 5.5×4 cm, 4×3 cm, and 2.5×2 cm, respectively. A brown back mole was observed over the occipital swelling, with blackish-blue discoloration evident on the rest of the swellings [Table/Fig-2c]. FNAC was performed on all three swellings, revealing morphology similar to the histopathology. Smears were highly cellular and displayed a dual population of cells. One population consisted of spindled cells with elongated nucleoli prominent nucleoli, and a scant amount of cytoplasm [Table/Fig-2d], while the other population showed round to oval cells, with a few plasmacytoid cells scattered singly, as well as in focal pseudoacinar formations, bearing dispersed chromatin, prominent nucleoli, and a moderate amount of cytoplasm. Occasional multinucleated giant cells were also evident. Numerous pigment-laden macrophages were identified in the background [Table/Fig-2e,f].



[Table/Fig-2]: a) Tumour cells positive for S100 (IHC; 200x); b) Tumour cells immunoreactive for HMB-45 (IHC; 200x); c) Clinical picture of child with multiple cervical swellings; d) FNAC from cervical swelling showing dual population of cells comprising of spindled cells with spindled nuclei and other population showing round to oval cells (MGG; 200x); e) FNAC from occipital swelling showing round to oval cells with few plasmacytoid cells scattered with dispersed chromatin and prominent nucleoli and moderate amount of cytoplasm along with pigment-laden macrophages. Inset showing a multinucleated giant cells (MGG; 200x); f) FNAC from cervical swelling showing round to oval cells with high N:C ratio scattered in pseudoacinar formations (inset) along with pigment-laden macrophages (MGG; 200x).

On follow-up, it was reported that the patient had not undergone any treatment and at the time of writing this paper, had not developed any more swellings.

DISCUSSION

The CCSST is an extremely rare and aggressive tumour, accounting for 1% of all soft-tissue sarcomas. Although the origin of these tumours is still unknown, they are said to originate from neural crest cells [1]. These tumours are relatively small (<5 cm) and can present between the ages of 7-83 years (median 27 years), with only 2% occurring in children younger than 10 years. They are more commonly seen in Caucasians than in African Americans or Asians, with a male to female ratio of 1:1 [2,3]. The tumour has a high propensity for local recurrence, regional and distant lymph node metastases. While it tends to involve the deep soft tissue of the upper and lower extremities, trunk, or limb girdle close to the

tendon, fascia, or aponeuroses in adults, the paediatric population has shown rare sites like the abdomen and scapula [4,5].

The CCSST is also known as “MM of soft part” due to its similar histological and IHC features with MM [6]. Both CCSST and MM are associated with a high frequency of lymph node metastases, the presence of melanin, ultrastructural evidence of melanosomes, and IHC staining for S-100 protein and melanoma-associated antigen (Melan-A) and HMB-45. However, these two are different entities on the molecular level. Most CCSSTs are characterised by a recurrent chromosomal translocation, t (12; 22), resulting in fusion of the Ewing Sarcoma (EWS) gene on 22q12 with the ATF1 gene on 12q13. Another translocation, EWS Ribonucleic Acid (RNA) binding protein 1, cAMP Responsive Element Binding protein 1 (CREB1) t (2; 22) (q34; q12), is less commonly seen in CCSST. On the other hand, MM is known to be associated with activating mutations in the v-raf murine sarcoma viral oncogene homolog B1 (BRAF) gene [4]. Its occurrence is found in relatively young adults and adolescents [5].

The CCSST was initially described by Dr. Franz Enzinger in 1965 as a distinctive tumour with peculiar clinical and histomorphological features that arise from the tendons and aponeuroses of the extremities [7]. This tumour is also known as “MM of soft parts,” a term coined by Chug and Enzinger due to its histomorphological similarity with MM. They demonstrated melanin in 72% of CCSST cases, depicting its origin from neural crest cells [1,6]. Both tumours are aggressive and share common IHC markers [1].

The origin of CCSST is from tendon sheaths and aponeuroses. The majority of the lesions are present in the extremities (82.69%), particularly in the lower limbs around the foot and ankle [4,8]. A few primary CCSSTs are also described in the chest wall and scapular soft tissues. Rarely, the kidney, trunk, penis, GIT, head and neck, lumbar region, parapharyngeal tissue, and penis are sites of affliction [1]. The tumour is more common in Caucasians, and men and women are equally affected with a median age of 27 years. Only a handful of cases are reported in children as the index case [1,2,8].

Despite several studies, the cause of this tumour remains unknown. However, genetic predisposition, radiation therapy, lymphoedema, gene mutations and prior chemotherapy are some risks associated with the occurrence of CCSST [1]. It presents as a slowly progressive mass but can suddenly become aggressive and metastasise, as in the index case which developed metastasis in a span of only eight months [6]. Because intratumoral calcifications are rare, these cases are usually reported as some benign-looking, well-defined homogenous mass akin to the present case, reported as a sebaceous cyst. On T1-weighted Magnetic Resonance Imaging (MRI), these lesions are usually homogenous and isotense or slightly hyperintense to muscle, whereas on T2-weighted MRI, they are usually more heterogeneous and show variable signal intensity. Due to the presence of melanin and iron, foci of hypointensity may be present [2].

These tumours grossly appear as a firm, tan-gray mass with a size ranging from 1-15 cm [1,4]. On microscopy, the neoplastic cells are polygonal and fusiform with a round, centrally located nucleus and abundant clear to eosinophilic cytoplasm, arranged into compact nests, lobules, fascicles, or haphazardly infiltrating the connective tissue. Dividing the lobules, a fine fibrocollagenous framework of variable thickness is generally seen that is contiguous with the connective tissue of adjacent tendons or aponeuroses. The clear-cell appearance is due to glycogen, which can be demonstrated by periodic acid-Schiff stain. Scattered multinucleated giant cells, pigment-laden or unpigmented melanosomes and areas of focal necrosis are also commonly seen. The cells display minimal pleomorphism. Diminished mitotic activity is seen in the

slowly progressive tumour [1,2]. IHC shows positivity for antigens associated with melanin synthesis such as HMB-45 and S100 within the cytoplasm and nucleus. Other markers like Cluster Differentiation 99 (CD99), Melan-A, neuron-specific enolase, vimentin, neuroendocrine markers such as synaptophysin, CD56, and CD57 can show variable positivity. However, cytokeratin, epithelial membrane antigen, carcinoembryonic antigen, desmin and Spinal Muscular Atrophy (SMA) are negative [1].

The tumours located in close proximity to tendons and aponeuroses are the main differentials of this tumour, such as paraganglioma-like dermal melanocytic tumour, MM, Malignant Peripheral Nerve Sheath Tumour (MPNST), Synovial Sarcoma (SS) and clear cell myomelanocytic tumour [1,8]. Other important differentials include melanotic schwannoma, Perivascular Epithelioid Cell neoplasms (PEComas), cellular blue nevus, SS, Alveolar Soft Part Sarcoma (ASPS), epithelioid sarcoma and carcinomas [2,6].

Though CCSST is thought to be a subtype of MM due to major histological similarities and the presence of similar melanosomes on electron microscopy, the two entities are genetically distinct and can be distinguished by their presentation and molecular markers. While CCSST usually occurs in a younger age group and is located in deeper tissues associated with aponeuroses or tendons (lacking cutaneous/epidermal involvement) unlike in MM. The characteristic t(12;22)(q13-14;q12) translocation is not seen in MM, which can be demonstrated by Fluorescence In Situ Hybridisation (FISH) or Reverse Transcription-Polymerase Chain Reaction (RT-PCR) [1,4,6].

In a study conducted by Hocar O et al., an attempt was made to analyse the genes associated with MM in cases of CCSST. It was seen that no mutation of the BRAF or Neuroblastoma RAS (NRAS) gene was identified in 95.54% of the analysed tumours. The rest of the tumours harbouring mutations in the BRAF and NRAS gene also presented the ATF1-EWS fusion gene and were considered atypical [2,4]. Besides these characteristics, CCSST has remained genomically uncharacterised. Copy number analysis of human CCSSTs has also shown frequent amplifications of the Microphthalmia-associated Transcription Factor (MITF) locus and chromosomes 7 and 8 [9].

The second major differential diagnosis of clear cell sarcoma will include clear cell carcinoma, such as hyalinising clear cell carcinoma; however, carcinomas are readily diagnosed by IHC, which should show a positive cytokeratin stain [10].

Synovial sarcoma and CCSST are molecularly distinct entities, other than the lack of melanocytic markers; SS shows a t(X;18)(p11.2;q11.2) translocation producing SYT/SSX1 or SYT/sSSX2 gene fusion, which is not seen in CCSST [1]. Paraganglioma-like dermal melanocytic tumour primarily presents in the extremities of female patients as a dermal nodule. On microscopy, it shows oval cells arranged in nests (zellballen pattern), separated by prominent fibrovascular stroma [8]. Clear Cell Myomelanocytic Tumor (CCMT) belongs to a family of tumours known as the perivascular epithelioid cell family of tumours, which commonly present in the abdomen, usually in the ligamentum teres of the liver of young patients. The tumour cells of CCMT show positivity for HMB-45 and smooth muscle actin but are negative for S-100 protein, Melan-A, desmin and pancytokeratin [1,11]. MPNSTs usually arise within large peripheral nerves and are negative for HMB-45 [12].

Additional supportive findings for the case to be a primary CCSST are that the lesion was solitary at the time of initial presentation and presented later with metastasis, only in the cervical lymph nodes draining from the scalp mass. These findings illustrate the typical spread of clear cell sarcoma from a primary site to regional lymph

nodes. Secondly, there was an absence of malignancy elsewhere in the body, thereby supporting the diagnosis of a primary clear cell sarcoma arising from the scalp swelling. Molecular and cytogenetic study was not done in the patient due to the unavailability of the tests in the institution and the poor socio-economic background of the patient. To the authors knowledge, this is the first report to describe a case of primary clear cell sarcoma of the scalp swelling in a child.

Though surgery is the treatment of choice for these tumours, they tend to recur with a local recurrence rate of 84% and late metastases in up to 63%. For localised lesions, wide surgical resection with negative margins is the mainstay of treatment. If complete excision is achieved, adjuvant therapy is unnecessary as there is no significant improvement in survival. Radiotherapy may improve outcomes in patients who undergo close resection margins. Chemotherapy is primarily employed in patients with metastatic disease [1,5,6]. Targeted therapies such as receptor tyrosine kinase inhibitors and histone deacetylase inhibitors, given in clinical trials, have shown benefit in some patients with this high-grade sarcoma [6]. Immune checkpoint inhibitors are the novel therapeutic agents and are under phase II clinical trials for CCSST [5]. After surgical excision, patients should be followed closely due to the high rates of recurrence. The five year and ten year overall survival for clear cell sarcoma is estimated to be 50% and 38%, respectively [1,4].

CONCLUSION(S)

The occurrence of CCS at a rare site and age group can pose a diagnostic dilemma for clinicians. Identifying the clinicopathologic pattern and differentiating it from MM and other benign conditions can prevent misdiagnosis. The present case report represents the first reported occurrence of clear cell sarcoma in a child in the scalp that was misdiagnosed as a sebaceous cyst. Prompt diagnosis and identification of this entity can prevent fatal consequences.

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