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An atypical chondroid syringoma with malignant degeneration: Utility of comparative genomic hybridization in confirming the diagnosis

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Abstract
Chondroid syringoma (CS) represents the cutaneous counterpart of mixed tumor (pleomorphic adenoma) of salivary glands. Definitive diagnosis is made on histopathology and is based on the presence of characteristic epithelial and stromal components. We report a case of an atypical CS arising on the extremity of an elderly male patient. Histomorphologic features of necrosis and cellular atypia raised suspicion for malignant degeneration, an exceptionally rare circumstance in this context. To further support the diagnosis of malignancy, array comparative genomic hybridization was performed from both low and higher grade areas of the tumor. Both regions demonstrated multiple copy number gains and losses, with additional loss of q7p (TP53), loss of 19p, and loss of heterozygosity on16q demonstrated in the more atypical foci. To our knowledge, this is the first case description of malignant degeneration of a CS with correlative microarray analysis. The findings in this case may prove useful in confirming the diagnosis in future ambiguous cases.

KEYWORDS
chondroid syringoma, comparative genomic hybridization, mixed tumor

INTRODUCTION
Chondroid syringoma (CS; also known as cutaneous mixed tumor) is a benign cutaneous neoplasm of sweat gland origin consisting of both epithelial and mesenchymal components. It bears morphologic and genetic resemblance to pleomorphic adenoma, the most common tumor of the salivary glands. Features that contribute to a diagnosis of CS include monomorphous epithelial cells arranged in cords and tubules with a peripheral myoepithelial layer, and occurring within a myxoid or chondroid stroma. Other variably present features include foci of squamous differentiation and keratocyst formation, fat metaplasia, and bone formation. Recently it was discovered that some CSs may harbor fusions in PLAG1, similar to those seen in pleomorphic adenoma. Atypical and malignant forms of CS have been described, though due to the uncommon nature of these tumors, reliable diagnostic criteria on histomorphology are a matter of debate. Moreover, the molecular events leading to malignant CS are largely unknown. Interestingly, there have been cases of CS with a deceptively bland cytological appearance (analogous to so-called benign metastasizing pleomorphic adenoma) that have later proven to behave in a malignant fashion. In this report, we describe a case of malignant CS arising within an atypical CS in which array comparative genomic hybridization (aCGH) was found to be especially useful in supporting a diagnosis of malignancy. To our knowledge, this is the first report describing cytogenetic alterations in atypical and malignant CS.

CASE REPORT
An 84-year-old Caucasian male with the past medical history of diabetes and hypertension presented with a slow-growing mass on his right...
upper extremity near the axilla that had been present for seven years. On physical examination, a $9 \times 7$ cm subcutaneous nodule was seen at the anteromedial aspect of the right arm. Excision of the mass was recommended given its large size, though the clinical impression was initially that of a lipoma.

Gross examination revealed a $7.5 \times 7 \times 4$ cm multilobulated mass with a thin pseudocapsule. The cut surfaces ranged from pink-tan and indurated to red, soft, and hemorrhagic (Figure 1). Microscopically, sections revealed a bulky proliferation of epithelial cells arranged in large clusters and solid cords, embedded in a myxoid and fibrous stroma (Figures 2 and 3). A surrounding rim of fibrosis was observed, with the tumor cells seen expanding the dermis and bulging into the subcutis. A large proportion of the epithelial cells had associated cytoplasmic vacuolation and clear-cell morphology (Figure 4). Focal gland formation and areas of chondroid matrix were appreciated.

In the more central and deeper portions of the tumor, areas of cystic degeneration and necrosis, irregular gland formation, cellular atypia, and mitotic activity were identified (Figure 5). An extended panel of immunohistochemical stains was performed. The cells of interest were positive for Sox10, CK7, INI-1, S100, AE1/3 and GATA (patchy), and were negative for hepatocyte antigen, PAX8, CK20, CD31, HMB45, Melan A and CD34. Taken together, these findings were consistent with a CS with atypical features worrisome for

![FIGURE 1](image1) Gross findings: Pseudoencapsulated multilobulated subcutaneous nodule with considerable hemorrhagic necrosis

![FIGURE 2](image2) Variably sized blue nodules are seen expanding the dermis and are enveloped in fibrosis (H&E, ×15)
malignant degeneration. As the lesion was dissected out from surrounding normal tissue, margin status could not be determined microscopically.

A diagnosis of malignancy was favored based on histomorphological features alone; namely, the large size, degree of necrosis, presence of areas with increased mitotic activity, cellular

FIGURE 3  The tumor is seen bulging through the subcutis and contains numerous cystic foci along with considerable necrosis (H&E, ×15)

FIGURE 4  Numerous interlacing cords/whorls of basophilic cuboidal-polygonal cells are seen embedded in a myxoid and hyaline stroma (top panel, H&E, ×100). On higher power, mucinous foci (bottom left panel, H&E, ×400) along with clear-cell cytomorphology is evident (bottom right panel, H&E, ×400)
FIGURE 5  Areas of tumor demonstrating cystic degeneration and necrosis (top panel, H&E, ×100). On higher power, mitotically active basophilic-pale cuboidal cells are seen forming irregular glandular structures and linear cords. Increased nuclear hyperchromasia, pleomorphism, and apoptotic forms are also evident (lower panel, H&E, ×400).

FIGURE 6  Microarray plot. Top panel represents lower grade areas of the tumor corresponding to the photomicrographs in Figure 4. Lower panel represents the more atypical areas of the tumor corresponding to the photomicrographs in Figure 5. Lower panel with additional copy number changes indicated by the red bar.
atyphia, and the identification of highly irregular glandular structures. However, a small degree of doubt was raised based on the lack of discernible host tissue invasion and the possibility that the necrosis was procedure-induced/trauma-related. Therefore, aCGH was performed from two separate regions within the tumor: (a) more conventional-appearing low grade area (top plot, Figure 6) more atypical-appearing higher grade area (lower plot, Figure 6). Multiple copy number gains and deletions were identified in both sampled areas, consistent with atypical/unstable tumor clones. Specifically gains were seen in 1p22.2p22.1, 1p21.3p21.2, 1p21.1p13.2, 1q21.1q23.3, 4p16.3q35.2, 16p13.3q22.1, 16q22.1q24.3, 22q11.1q13.33, with losses seen in 1q32.2q44, 6p25.3q27, 8q12.1q12.2, 12p13.33, 12q12q14.2, and Xq28 (homozygous loss). The deletions seen at 8q12 and 12q12 regions further supported the diagnosis of a myoepithelial neoplasm. Additionally, the more atypical portion of the tumor demonstrated evidence of clonal evolution with additional loss of 17p13.3p11.2 (TP53), loss of 19p13.3p13.11, and loss of heterozygosity (LOH) on 16q11.2q24.3. Based on this additional information, a low-grade malignant CS was the favored diagnosis. Correlation with intraoperative findings was recommended to ensure that the tumor was adequately excised. A positron emission tomography-computed tomography scan failed to reveal any evidence of metastatic disease. After discussion of the potential risks/benefits with the patient, the decision was made to forgo a wider excision and to proceed with close clinical surveillance alone. The patient has remained free of detectable recurrence for seven months.

3 DISCUSSION

CS is considered a rare tumor of sweat glands, first described by Hirsch and Helwig in 1961. The reported incidence of CS is 0.01% to 0.098%. Although there is no distinct clinical feature to aid in definite diagnosis, it usually presents as a firm, asymptomatic, skin colored, slow-growing, solitary dermal, or subcutaneous nodule. The typical size ranges from 0.5 to 3 cm. The most common site of involvement is the head and neck, and it predominantly affects middle-aged men.

Histopathologically, the lesion is characterized by an admixture of epithelial and mesenchymal elements; hence the term “mixed tumor.” The proposed histopathologic criteria by Hirsch and Helwig included five features: (a) nests of cuboidal or polygonal cells; (b) intercommunicating tubuloalveolar structures lined with two or more rows of cuboidal cells; (c) ductal structures composed of one or two rows of cuboidal cells; (d) occasional keratinous cysts; and (e) a matrix of varying composition. The stroma exhibits varying density and can be chondroid, myxoid, fibrous, hyaline, or osseous. The ductal and tubuloalveolar structures consist of two types of cells: the darker, cuboidal to polygonal cells lining the inner layer of these structures exhibit epithelial lineage, whereas the light, low-cuboidal cells forming the outer layer of these tubular and ductal structures manifest myoepithelial differentiation. Varella-Duran et al proposed the pluripotentiality of the myoepithelial cells, citing their role in the production of the chondroid areas of the tumor. Later on, Mills determined that CSs are clonal neoplasms consisting of replicating cells with the potential to differentiate toward epithelial or mesenchyme, which explains the tremendous diversity in histopathologic appearance.

The malignant variant of CS is extremely infrequent and may arise from malignant transformation of an otherwise ordinary CS. Features previously attributed to malignant CS include a greater propensity to occur on the extremities, larger size, the presence of cellular atypia and increased cellularity, increased mitotic rate, invasion of surrounding tissue, and tumoral necrosis. Metastasis to regional lymph nodes, as well as to distant sites such as bone and visceral organs, has also been described. The term “cutaneous mixed tumor with atypical features” was previously proposed for tumors with architectural features of malignancy, though without evidence of metastasis. Wide excision of the primary tumor is generally regarded as the preferred treatment for the primary tumor, with radiation therapy and chemotherapy potentially having a role in the setting of metastasis (though the optimal efficacious systemic therapy is unknown given the rarity of the tumor overall and lack of randomized controlled trials).

Progressive accumulation of genomic changes is a crucial step in the alteration of normal biological mechanisms and eventual development of malignancy within a tumor. aCGH is a molecular cytogenetic technique used in detecting chromosomal abnormalities and locating regions of genomic imbalances. Results from our aCGH assay further confirmed the lineage of the tumor by identifying early known genetic events. In the context of myoepithelial neoplasms, such as CS and pleomorphic adenoma, deletions of the 8q21 region and the 12q12q14.2 regions are commonly reported findings. The 8q21 loss results in the loss of the first exon of the PLAG1 gene and is most consistent with a PLAG1 gene (nuclear oncoprotein) rearrangement with an unknown partner gene resulting in PLAG1 overexpression. The loss of 12q12q14.2 results in dysregulation of the HMGA2 gene, which encodes for a transcriptional gene regulator.

Furthermore, our results show that aCGH may have a role in the clinical setting when faced with a CS with atypical features to help support or refute a diagnosis of malignant degeneration. This may be particularly useful when only some, but not all the morphologic features of malignant CS are identified on prepared sections or when there is considerable atypia confined focally within the lesion. In this case, the presence of considerable copy number changes (n = 14) combined with the morphologic atypia observed and demonstrable clonal evolution with loss of 17p (TP53) and LOH on 16q (likely reflecting loss of another tumor suppressor gene) support a diagnosis of malignant transformation. In particular, loss of TP53 is known to be associated with disease progression and an adverse prognostic impact in multiple settings including other cutaneous adnexal neoplasms. Additional larger studies examining the cytogenetic changes in benign CS, atypical CS, and bona fide malignant CS are needed before firm conclusions can be drawn regarding the exact number/threshold or consistent genetic events that are associated with aggressive behavior in this context.
4 | MATERIALS AND METHODS

4.1 | Summary of cytogenetic analysis

Following review by a pathologist, 10 slides were cut at 10 μm thickness from a representative formalin-fixed and paraffin-embedded (FFPE) tissue block and tumor was macrodissected using a H&E-stained slide as a guide. DNA was extracted and purified according to the manufacturer’s protocols (Qiagen QiAmp DNA Mini Kit). Extracted DNA was quantified following the manufacturer’s instructions and diluted to a final concentration of 12 ng/μL with a total of 80 ng utilized. Chromosomal microarray analysis of tumor samples was performed using the OncoScan FFPE Assay, which utilizes Molecular Inversion Probe (MIP) technology to obtain accurate genome-wide copy number and LOH profiles. The assay contains 22 000 probes across the genome and targeted cancer regions, allowing for detection of copy number abnormalities at 50 to 100 kb resolution in ~900 cancer genes and at 300 kb resolution in other chromosomal regions. Patient hybridization results are compared to data derived from over 300 FFPE samples from unaffected tissues. All data were analyzed and reported using the February 2019 Genome Reference Consortium Human Build 38 patch release 13 (GRCh38.p13).

4.2 | Reportable range

Deletions larger than 1 megabase, duplications larger than 2 megabases, and copy neutral LOH larger than 5 megabases are generally reported; however, complex genomic alterations may be reported in aggregate, and well-documented pathogenic constitutional and/or acquired abnormalities of any size may also be reported. The genome coordinates described are best estimates and may not represent precise breakpoints, especially for abnormalities detected in a low percentage of cells. The detection threshold for mosaicism is variable, depending on the size of the segment. Common population number variants cited in the Database of Genomic Variants are not reported.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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