

# A Rare Case of Multiple Segmental Eccrine Spiradenomas

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## ABSTRACT

Eccrine spiradenoma is a benign adnexal neoplasm that has been historically designated as a tumor of eccrine differentiation, although current reconsideration indicates an apocrine process. It usually presents on the trunk and extremities as a tender dermal or subcutaneous papule or nodule frequently with a pink or blue hue. The clinical picture is often not distinct and biopsy is required for diagnosis. Eccrine spiradenoma can present in a variety of ways, including as tumors arranged in zosteriform/dermatomal and/or blaschkoid distributions, often precluding a straightforward diagnosis. Proper diagnosis of eccrine spiradenoma is important due to the occurrence of potentially life-threatening malignant transformation. This article illustrates a rare presentation of eccrine spiradenoma with a concise review for the dermatologist. (*J Clin Aesthet Dermatol.* 2011;4(4):38–44.)

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**E**ccrine spiradenoma (ES), first described in 1956, is an uncommon, benign, dermal tumor of apocrine differentiation derived from cutaneous sweat glands.<sup>1</sup> It classically presents in the 2<sup>nd</sup> to 4<sup>th</sup> decades of life as a small, painful, grey to pink nodule on the upper ventral aspect of the body. Most presentations of ES are solitary, comprising more than 97 percent of cases. The incidence of ES is roughly equivalent in men and women.<sup>2–4</sup> Multiple ES is a rare phenomenon, comprising less than two percent of all cases and appears to be predominant among women.<sup>5,6</sup> Approximately 37 cases of multiple ES, including those in zosteriform/dermatomal and/or blaschkoid distributions, have been reported in the literature.<sup>2,4,6–28</sup> Given the rarity of multiple ES in a linear distribution and the uncommon risk of malignant transformation, the authors present this case for interest, review, and awareness.

## CASE REPORT

A 55-year-old Caucasian man presented to the authors' outpatient dermatology clinic complaining of a 20-year history of painful lesions on the right chest and arm. Of

patient concern, the lesions were recently more painful and had increased in size and number. His past medical history was unremarkable. He denied any family members with similar skin findings or any history of skin cancers. Physical exam revealed multiple, well-circumscribed, subcutaneous, blue-grey nodules in a dermatomal distribution across the right chest and arm (Figure 1). The nodules were tender, firm, and fixed to the overlying skin and ranged in size from 0.5 to 6cm in diameter. Surgical excision of the most prominent, painful nodule of the right arm was sent for histological analysis (Figure 2).

Histological findings demonstrated sharply delineated dermal nodules comprising basaloid cells arranged in a trabecular pattern surrounded by eosinophilic fibrous strands (Figures 3a–3b). Small, dark, basaloid cells with hyperchromatic nuclei, larger cells with pale nuclei in the center of the clusters, and numerous scattered lymphocytes were also seen throughout, consistent with a diagnosis of ES (Figure 4). Typical spiradenoma features, as well as small areas with a cylindroma-like “jigsaw puzzle” pattern, were also appreciated. No evidence of malignant transformation was noted.

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**Figure 1.** Multiple, well-circumscribed, subcutaneous, blue-gray nodules of various sizes in a segmental distribution across the right chest and arm



**Figure 2.** A large, well-circumscribed nodule over the right arm as seen during excision

The patient underwent surgical excision with complex, linear closure of multiple chest and arm nodules given the significant pain experienced while wearing a seatbelt during driving. Excellent cosmetic and functional results were seen and the patient was advised to return for future excisions in the case of increasingly painful or rapidly growing lesions. While there was no evidence of malignant transformation in this patient, continuous follow up is necessary given the rapid evolution and possibility of malignant transformation within long-standing lesions.

## DISCUSSION

**Introduction.** Few cases of multiple ES have been reported in the literature to date. The present case is a unique presentation of multiple ES in a pattern following the T1 dermatome (Figure 1). In cases of multiple ES, it has been proposed that an abnormal clone of multipotent stem cells of the folliculosebaceous-apocrine unit arise during embryogenesis subsequently producing a proliferation of abnormal cells resulting in nodule formation and possible malignant transformation.<sup>29-33</sup> Histological findings are often consistent with ES and cylindroma within the same biopsy as many tumors show overlapping features of these two entities.<sup>12</sup> It may be that these two entities represent two extremes on a continuous spectrum of dermal tumor originating from a common progenitor.<sup>34</sup> Spiradenomas occurring in multiplicity and in concert with cylindroma or trichoepitheliomas should prompt investigation into a diagnosis of Brooke-Spiegler syndrome.

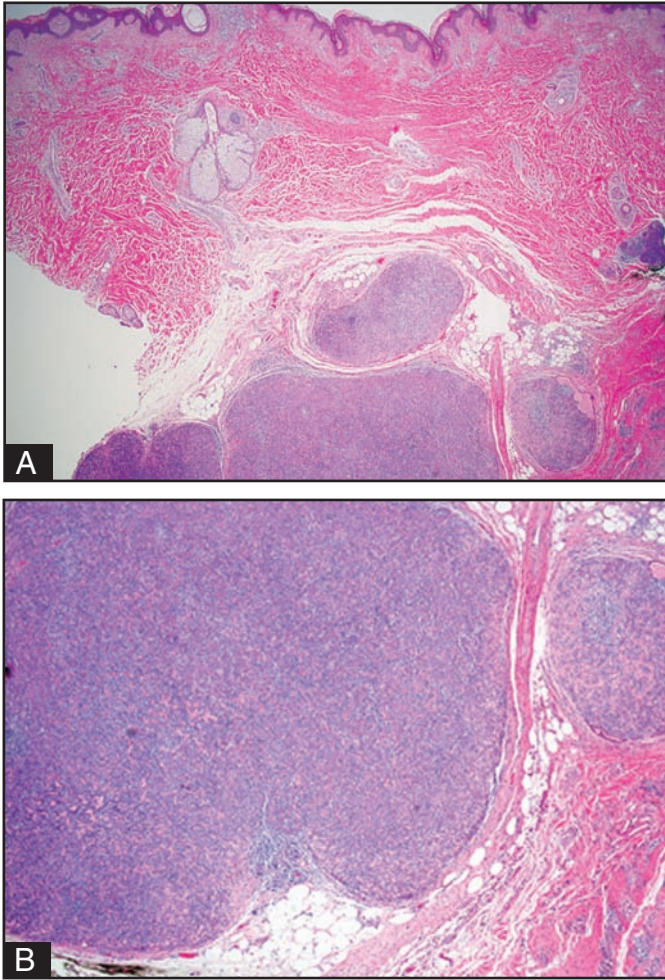
Brooke-Spiegler syndrome is an uncommon autosomal dominant disorder characterized by a high affinity to form multiple adnexal neoplasms, especially trichoepitheliomas, cylindromas, and spiradenomas.<sup>35</sup> The occurrence of both follicular and apocrine differentiation may represent

separate paths of maturation from a single germ cell, explaining how several types of tumor coexist. In fact, germline mutations in the cylindromatosis (CYLD) gene have been described in families with cylindromas, trichoepitheliomas, and spiradenomas.<sup>36</sup> Recently, the CYLD gene has been recognized as an important tumor suppressor gene with a prominent role in the regulation of nuclear factor kappa-beta (NF- $\kappa$ B), a transcription factor that promotes cell survival and oncogenesis.<sup>37,38</sup> Thus, defective tumor suppression genes seem to be important in the development of spiradenomas.

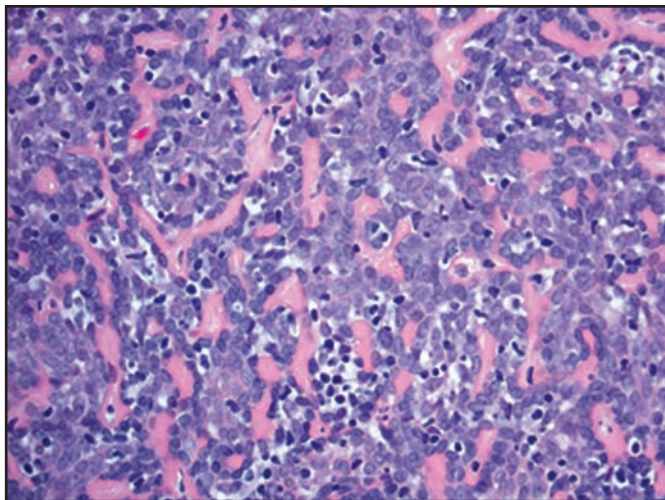
Benign ES generally comprises lesions ranging from 0.5 to 3cm in diameter that remain chronically stable.<sup>39,40</sup> Malignant transformation is rare and occurs more often in cases of multiple benign ES than in solitary cases.<sup>39</sup>

Malignant ES, first described in 1972, is thought to arise from transformation of a long-standing, benign ES.<sup>30</sup> *De-novo* cases have recently been reported in the literature.<sup>41</sup> No age, gender, or site predilection has been described, and malignant transformation generally occurs 20 to 30 years after initial lesion detection.<sup>39</sup> Many mechanisms have been proposed, such as trauma, but none are substantiated in the literature.<sup>42-44</sup> In these rare cases of malignant potential, p53 may be increased even in the presence of a benign-appearing histology.<sup>45,46</sup> Malignant ES are aggressive tumors that spread both hematogenously and lymphogenously and have been reported to have a mortality of 39 percent if left untreated.<sup>43,44</sup> Since the rate of metastasis is close to 50 percent and can result in death, these patients must be followed closely. Currently, no guidelines have been developed for surveillance in patients with multiple ES, although it seems reasonable that patients with larger-sized, multiple, and/or symptomatic lesions be monitored regularly.

**Etiology.** The exact etiology of ES still remains



**Figures 3A and 3B.** A) Overlying normal epidermis with underlying multiple, well-circumscribed, dermal nodules consisting of basophilic cells (hematoxylin-eosin [H&E], magnification 20X). B) Increased powered view of a dermal nodule with cords of basaloid cells arranged in a trabecular pattern with eosinophilic fibrous strands and numerous lymphocytes (H&E, magnification 40x).



**Figure 4.** High-powered view demonstrating small, dark, basaloid cells with hyperchromatic nuclei, larger cells with pale nuclei in the center of the clusters, and numerous scattered lymphocytes seen throughout (H&E, magnification 100x)

controversial. ES has never been observed on glabrous skin, as it is an undifferentiated or poorly differentiated benign adnexal neoplasm historically designated as a tumor of eccrine lineage. However, both ES and cylindroma can sometimes display tubular differentiation with a “decapitation” pattern as would be expected in an apocrine neoplasm.<sup>47,48</sup> Thus, recent assessment has indicated an apocrine process. As previously described, ES commonly occurs jointly with other cutaneous appendage tumors, such as cylindroma, trichoepithelioma, and trichoblastoma, which points toward the development of folliculosebaceous-apocrine lineage rather than eccrine differentiation.<sup>49,50</sup> Further, if ES were truly eccrine, occurrence on the palm or sole would be paramount rather than rarely seen. In Brooke-Spiegler syndrome, a defective tumor suppressor gene, *CYLD* on chromosome 16q, results in numerous cutaneous appendage tumors suggesting kinship rather than disparate lineages.<sup>46,51</sup> The most recent hypothesis is suggestive of an abnormal multipotent stem cell in the folliculosebaceous-apocrine unit, although some reports have suggested trauma as the inciting factor.<sup>43,52</sup> p53 expression in malignant ES is also suggestive of an underlying abnormality of tumor suppression or innate surveillance, but the significance of this observation is currently unclear.

**Presentation.** ES classically presents as a dermal or subcutaneous papule or nodule that can range in size up to many centimeters. A pink or blue hue overlying the nodule is suggestive, but clinical diagnosis alone cannot give accurate diagnosis. ES are often painful and are in the differential diagnosis of painful dermal tumors (as described by Naversen et al<sup>53</sup>) characterized by the popular mnemonic “LEND AN EGG,” which stands for leiomyoma, ES, neuroma, dermatofibroma, angioliopoma, neurilemmoma, endometrioma, glomus tumor, and granular cell tumor.<sup>54</sup>

No clear categorization exists for the multitude of presentations of ES. Rarely, ES presents as multifocal or multiple localized tumors arranged in a linear, zosteriform, or nevoid distribution. A recent case report and review proposed a system of categorization based on both clinical and histological findings.<sup>6</sup> Clinically, they defined the lesions as solitary or multiple, with further distinction to describe the clinical appearance and define the distribution/pattern (linear, zosteriform, nevoid, or blaschkoid). Histologically, the authors focused on determining whether the lesions were benign or malignant, and they identified three histological classifications: common, vascular, and cystic.

A simple system of clinical characterization comprises descriptors based on quantity, location, and distribution. Quantity indicates whether the lesion is solitary or in multiplicity. Location denotes whether the presentation is multifocal, present at various body sites, or localized and isolated to a particular area. Distribution describes how the lesions are configured or arranged in the previously described location. Distribution can be zosteriform/dermatomal, blaschkoid, or linear. Zosteriform is a term used to describe lesions that resemble herpes zoster, which often follows a dermatomal distribution. Dermatomal refers to a

distribution along a dermatome (or series of dermatomes) corresponding to an area of skin innervated by site-specific spinal nerves. Thus, zosteriform and dermatomal are similar and together refer to a band-like unilateral skin lesion along a cutaneous distribution of a spinal nerve(s). In contrast, a blaschkoid pattern follows the lines of Blaschko, a surface pattern invisible under normal conditions and thought to represent pathways of epidermal cell migration and proliferation during embryological development (genetic mosaicism). They follow a “V” shape over the back and an “S” shape over the chest, stomach, abdomen, and head/neck and appear as whorls typically seen in pigmentary disorders, X-linked genetic disorders, or acquired inflammatory skin conditions. In the literature, the terms “blaschkoid” and “dermatomal” have been mistakenly used interchangeably. Lines of Blaschko do not correspond to nervous, muscular, or lymphatic systems, and dermatomal lines are never in a whorled pattern. Linear is used to describe any lesions in a straight line system and is the most generic of the descriptors.

**Diagnosis.** The definitive diagnosis of ES consists of a skin biopsy; however, fine needle cytology has also been reported.<sup>55</sup> ES comprises large, sharply circumscribed, basophilic nodules (“cannon balls” or “blue balls”) arranged in intertwining cords, islands, or sheets in the dermis or subcutaneous tissue that are surrounded by a fibrous capsule.<sup>56</sup> Basaloid cells can be composed of two distinct morphologies with one cell type that is larger, pale, and with an ovoid nuclei and the other type that is smaller, dark, and with a compact hyperchromatic nuclei. Duct-like structures can be present at the center of the lesions, which often have scattered lymphocytes.<sup>4</sup> Strands of cells are positive for cytokeratin and the lumina are positive for carcinoembryonic antigen.<sup>57</sup> S-100 staining has been noted in ES and cylindromas attributed to eccrine differentiation. In cases where ES has co-expression of cytokeratin and smooth muscle actin, authors have suggested differentiation toward myoepithelial cells.<sup>58</sup>

Malignant ES is suspected in patients with rapid enlargement, an increase in number, change in color, or with the development of symptoms, such as pain, ulceration, or pruritus. Histological findings may include atypical cells, elevated mitotic counts, loss of the typical lobular pattern and dual cell population, rare foci of necrosis, and enlarged cells of one cell type on histological evaluation.<sup>2,44</sup> Additionally, tumor cells extending through the capsule into adjacent stroma are also suggestive.<sup>59</sup>

Immunohistochemistry can be useful in evaluating for malignant cases of ES. In a case of malignant ES of the breast, typical histological features were noted along with areas of adenocarcinoma, squamous cell carcinoma, and sarcoma with staining positive for the p53 protein.<sup>60</sup> Others have demonstrated that cells may express cytokeratins, epithelial membrane antigen, and p53.<sup>41</sup>

In 2000, Granter et al<sup>61,62</sup> divided malignant ES into two groups (high and low grade) based on clinical and histological features. High-grade malignant ES has more obvious features of malignancy with pleomorphism and

increased mitoses (4–32/hpf).<sup>44,61</sup> Low-grade malignant ES has less obvious features of malignancy, such as loss of the typical ductal cells, mild-to-moderate pleomorphism, and lower mitotic rates (2–10/hpf).<sup>44,61</sup> As explained previously, malignant ES tends to have a high rate of metastasis to regional lymph nodes, lungs, brain, and liver; therefore, radiological studies, such as x-ray, computed tomography (CT), or magnetic resonance imaging (MRI), are useful in assessing for metastatic foci.

**Differential diagnosis.** The diagnosis of ES can be elusive given its multiple presentations and frequent lack of skin surface changes. Correct diagnosis is critical due to the potential for malignancy. Popular pneumonics are used to describe painful dermal tumors as described above and these should all be taken into consideration on initial evaluation. While the following additional entities are not generally painful, trichoepithelioma, lipoma, cylindroma, and poroma should be considered in the differential given their similar presentations. Further, in long-standing lesions and those with symptoms or recent growth, malignant eccrine poroma, malignant nodular hidradenoma, and chronic ulcers should be considered depending on the presentation. One case report documents a toe ulcer followed for four years as a chronic nonhealing ulcer, but later found to be a malignant ES.<sup>63</sup>

The diagnosis can generally be easily distinguished histologically if the clinical picture is not distinctive. However, histological differentiation of cylindroma and ES is less straightforward. As a general rule, cylindromas tend to present on the head and neck and are usually not painful as compared to ES, which present on the trunk and extremities and are generally painful. Histologically, cylindroma is differentiated by the presence of basaloid cells arranged in “islands” that fit together like a jigsaw puzzle, rather than in “rosettes” as seen in ES.<sup>64,65</sup> Other histological distinctions include the presence of a densely eosinophilic PAS-positive material present around the tumor “islands” in the case of cylindroma, as well as the absence of scattered lymphocytes that are often present in ES.

**Treatment and management.** The mainstay of treatment for both benign and malignant ES is surgical removal, although this may not be necessary unless the lesions are cosmetically intolerable, painful, or increasing in size or number. Other options, such as radiotherapy, carbon dioxide laser ablation, or chemotherapy, are reserved for cases in multiplicity or that are malignant. Due to the potential for malignant transformation, wide surgical excision or Mohs micrographic surgery offers the most conservative treatment choice, and lesions treated tend not to recur. One author suggests a combination of surgical management (staged surgical resections with reconstruction using complex linear closures and random-pattern cutaneous flaps) and medical management (carbon dioxide laser) for good cosmetic results.<sup>34</sup>

For the treatment of malignant ES, no treatment has been routinely established as paramount. Resection with wide margins (1–3cm) down to the fascia with lymph node dissection has been described as the most accepted

treatment.<sup>41,66,67</sup> Radiation and chemotherapy have also been proposed, but no conclusive studies have substantiated optimal practice.<sup>39,43,66</sup> Hyperthermic limb perfusion chemotherapy has been tried as some believe that alterations of temperature may target treatment to tumor cells over healthy ones.<sup>68</sup> A recent meta-analysis of malignant ES demonstrated that patients with no metastasis who underwent surgical excision had a disease-free survival rate of 100 percent at 33 months.<sup>66</sup> In contrast, patients with distant metastases treated with either surgery alone or surgery and adjuvant chemotherapy had a median survival of 12 and 20 months, respectively. Despite the difference in median survival rates between the two groups, the results were not statistically significant. Resection of lymph node metastasis resulted in patients who were disease free at the final follow-up evaluation (mean 47 months) suggesting that, in the case of positive lymph nodes, surgical resection is certainly warranted. The authors concluded that aggressive surgical removal is necessary in cases of malignant ES with or without metastasis.<sup>66</sup>

In cases of malignant ES, close clinical follow up every three months the first year after resection, every six months the second year after resection, and annually thereafter is important given the possibility of recurrences. Due to the high rate of metastasis to the liver and lung, annual chest radiographs, liver function tests, liver ultrasound, chest and abdomen CT, and/or MRI may be useful.<sup>44</sup> But again, no consensus has validated these practices. Genetic counseling for cases of familial ES is also advised.<sup>34</sup>

## CONCLUSION

ES is a dermal tumor of the sweat glands and its etiology is yet to be clearly identified. ES may present *de novo* or congenitally in clinically diverse presentations. The diagnosis is very important because of the potential for malignant transformation, especially in cases of multiple or symptomatic lesions. While extremely rare, malignant ES can be lethal if undiagnosed and untreated, and a high index of suspicion is needed on any benign lesion that rapidly changes in characteristics or is consistent with long-standing disease. Treatments for ES have not been well established, but surgical excision is currently the gold standard with low rates of recurrence. Case reports and reviews describing interesting presentations of ES are important to maintain awareness and to help guide proper management.

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