Squamous Lesions of the Ovary

Etienne Mahe, MD; Monalisa Sur, MBBS, FCPath(SA), MMed(Wits), FRCPath(UK), FRCPC

The ovary shows an innate potential for markedly variable histogenesis, including squamous differentiation. Although not uncommon, squamous differentiation in ovarian lesions can be present in several diagnostic contexts, both benign and malignant. We present a review of the literature pertaining to squamous lesions of the ovary. In particular, we summarize the relevant clinical features, workup, gross findings and histopathologic features, differential diagnosis, treatment, and prognostic features of both the common and rare squamous entities found in the ovary.


When encountered in the ovary, a diagnosis of squamous cell carcinoma can pose a challenging differential diagnosis. Although squamous cell carcinoma is a frequent entity encountered in the female genital tract, it is rare in primary form in the ovary and, hence, when identified therein, it is incumbent on the pathologist to explore other potential entities or primary sites. Primary squamous cell carcinoma has been identified in the ovary, however, and as such, demonstrates the vast histologic heterogeneity that may be seen in ovarian lesions. This is a review of the literature pertaining to ovarian squamous lesions, including a number of diagnostic pearls.

DEFINITION

The identification of squamous elements in specimens of ovarian origin is generally straightforward. From a first principles perspective, the presence of architectural and/or cytologic features that recapitulate those found in squamous mucosae define squamous differentiation.1 In well-differentiated forms, squamous elements may show keratinization/keratinocyte maturation and intracellular bridging.2 Furthermore, the cytologic features of squamous cells seen elsewhere should be consistent, namely polygonal, eosinophilic cells, with central nuclei and 1 or 2 prominent central nucleoli.3 More challenging, poorly differentiated forms can be encountered, in which case, few reference characteristics may be identifiable; these cases may require ancillary immunohistochemical studies to help confirm the diagnosis. Rarely the histologic picture can be blurred by the presence of various architectural features suggesting different entities; the presence of pseudoglands, papillations, cyst formation, and polypoid and insular patterns can be confusing.3 In such cases, again, immunohistochemistry can be very helpful.

EPIDEMIOLOGY

Squamous elements are most commonly identified in the ovary as part of a mature cystic teratoma (or dermoid cyst).3,5 The mature cystic teratoma contains adult-type tissues from all 3 germ layers.4,5 Ectodermal tissues, however, are often predominant, and skin is commonplace.4 The squamous elements present in mature teratomas are benign in the resounding majority.4,5 Squamous cell carcinoma does arise from mature teratomas, however; this entity, in fact, is the most common malignant component arising from a mature teratoma.3 Although only 1% to 2% of mature teratomas harbor a malignant component, up to 80% of those will be of squamous derivation.4,6,7

Metaplasia is likely the next most common cause of squamous differentiation in the ovary. The most frequently encountered nonteratomatous primary tumors showing squamous differentiation are ovarian endometrioid adenocarcinoma of the ovary and the Brenner tumor.2 In each of these cases, the primary lesion most often has readily identifiable histologic features. Metastases are another common source of squamous elements in the ovary. Clement and Young3 suggest that endometrioid adenocarcinoma and squamous cell carcinoma of the cervix are 2 likely sources of metastatic ovarian squamous components. A few cases identified in the literature were found to have ovarian squamous elements arising in concert with previously or concomitantly identified cervical carcinoma in situ.5,9

Very rarely, squamous elements are identified in the absence of any of the above scenarios. Young et al10 have identified epidermoid cysts, some in concert with small Walthard rests, but in the absence of any other teratomatous features. Other case reports and small series11–13 have identified de novo squamous cell carcinoma of the ovary, some associated with endometriosis. By all accounts, these entities are exceedingly rare, and questions remain about their histogenesis.
CLINICAL PRESENTATION AND WORKUP

Dermoids generally raise clinical suspicion by way of a painless mass lesion; other manifestations relating to perforation, torsion, or infection may alter the clinical picture significantly. Otherwise the presence of a complex cystic structure with strands of hair can usually be easily identified. Regardless of the underlying etiology, squamous cell carcinoma of the ovary does not seem to have any pathognomonic imaging features. The radiologic findings generally show a solid and cystic mass, usually about 10 to 15 cm in maximal dimension. This latter fact may be helpful in sorting out the preliminary differential diagnosis, given that many aggressive ovarian neoplasms are much larger. Areas of necrosis are often visible, and there are often adhesions to surrounding pelvic structures.

Pelvic imaging is a mainstay in the workup of ovarian lesions. Dermoids can be easily recognized radiologically when bone or teeth are present. Otherwise the presence of a complex cystic structure with strands of hair can usually be easily identified. Regardless of the underlying etiology, however, squamous cell carcinoma of the ovary does not seem to have any pathognomonic imaging features. The radiologic findings generally show a solid and cystic mass, usually about 10 to 15 cm in maximal dimension.

Frozen sections are often requested at the time of surgery for intraoperative and postoperative planning. In cases of clinically suspicious malignant tumors, a diagnosis of squamous cell carcinoma can be made if all the required histologic features are present. The underlying etiology should not be determined by guesswork, however, given that extensive sampling of the surgical specimen is required to rule out the presence of a teratoma, an occult endometrioid carcinoma, or a Brenner tumor. With a diagnosis of squamous cell carcinoma of the ovary, full gynecologic staging should be undertaken, including completion of a total abdominal hysterectomy and a bilateral salpingo-oophorectomy, as well as peritoneal, omental, and lymph node biopsies as the case may dictate.

GROSS AND MICROSCOPIC FEATURES

Dermoid cysts are usually easily recognized grossly; often they are large and contain sebaceous material and hair. Other tissue types may be identified, including teeth, bone, adipose tissue, thyroid, and brain. With deference to the remarkable breadth of tissues that can be present in a teratoma, these cases generally do not present diagnostic challenges; however, even with clearly teratomatous features on gross examination, immature or malignant mature components may still be present. A recent review noted a previous study in which cases of invasive squamous cell carcinoma arising in dermoids were detected as such on intraoperative consultation only 50% of the time. Even dermoid cysts, therefore, should be diligently sampled, with careful focus paid to the solid components.

Epidermoid cysts are generally much smaller (ranging from 0.2 to 4.6 cm, according to Young et al) and do not show the same propensity for weird and wonderful contents. Chiefly, these cysts contain sebaceous material and show benign (noninvasive), keratinizing squamous epithelium on histologic examination. The presence of other tissue types in conjunction implies a teratoma.

Primary squamous cell carcinomas arising without a dermoid component tend to be smaller than other aggressive ovarian neoplasms. In the series of Pins et al, the squamous cell carcinomas without a dermoid component ranged in average size from approximately 10 to 12 cm. These lesions may have both solid and cystic components (see Figure 1), often with markedly thickened walls. Cyst contents may be sebaceous, and areas of necrosis may also be visible. Some reports note adhesion of such lesions to surrounding structures. Also, primary squamous cell carcinoma arising in endometriosis may show endometriotic cysts on gross examination. Histologic examination shows invasive squamous cells, in most instances, often with obvious keratin pearl formation (Figure 2). In their large case series, Pins et al noted several possible architectural patterns, in addition to the usual architecture of squamous cell carcinoma, including a spindle cell pattern. A pseudogland pattern was also noted in one case from our institution (see Figure 3). A search should be made for foci of endometriosis; for the purposes of classification, most authors recommend that the diagnosis of squamous cell carcinoma in association with...
endometriosis be reserved for those cases in which direct involvement of endometriotic foci by squamous carcinoma is noted (Figure 4); otherwise, a diagnosis of pure squamous cell carcinoma is appropriate.7

DIFFERENTIAL DIAGNOSIS

One primary issue, raised on detection of squamous elements in the ovary, is whether the lesion is invasive. In many cases, the gross appearance makes this question moot. Sometimes, however, careful histologic assessment for the classic features of invasion is required. These include anastomosing tongues or cords of tumor infiltrating a fibrous or desmoplastic stroma, infiltrating irregular and ragged clusters of neoplastic squamous cells, and reverse maturation (in which keratinization appears to progress in the reverse direction). Other more unusual variants may display so-called pushing border invasion; these can be especially tricky for inexperienced observers.

Other epithelioid lesions may enter the differential diagnosis, especially when considering squamous cell carcinomas that are less differentiated. Two entities should be mentioned: epithelioid mesothelioma and epithelioid sarcoma. These entities will generally show very bulky disease and can be segregated with help from a broad immunohistochemical panel.

ANCILLARY STUDIES

In most instances, a combination of clinical history, diligent gross examination, and microscopic evaluation by sections stained with hematoxylin-eosin will suffice to identify the underlying etiology of an ovarian squamous lesion. In some cases, however, unexpected architectural patterns or the identification of elements distinct from the primary component may underscore the need for ancillary studies. Immunohistochemistry is of greatest use; similar to other organ systems, squamous cell carcinoma of the ovary should show high-molecular-weight cytokeratin positivity (eg, cytokeratin 34βE12 or cytokeratin 5/6) as well as p63 positivity.20 If a metastatic lesion is suspected, an immunohistochemical panel with markers specific to the tissue of interest should be chosen. When other more common gynecologic tumors need to be excluded, a panel that includes vimentin, cytokeratin 7, estrogen receptor, p16, and p53 markers may be useful.20 In particular, these markers should help to exclude endometrioid adenocarcinoma. If a cervical primary is suspected, a panel that includes p16 as well as antibodies for common human papillomavirus serotypes may be helpful.20 It may also be prudent to exclude the possibility of an epithelioid mesothelioma or sarcoma. In the former case, calretinin and Wilms tumor-1 stains are helpful, both generally positive in mesothelioma.20 In cases of epithelioid sarcoma, a number of epithelial markers are required to confidently exclude a true epithelial origin. Finally, in cases in which suspicions of squamous cell carcinoma arising in endometriosis are raised, an iron stain may be helpful to highlight areas of previous hemorrhage and hemosiderin deposition.20

TREATMENT AND PROGNOSIS

Dermoid cysts can usually be adequately treated with limited surgical excision. This applies, likewise, to the rare cases of epidermoid cysts. In cases of primary squamous cell carcinoma of the ovary, regardless of the etiology, adjuvant treatment may also be attempted in addition to
radical surgical excision and staging. Some case reports have noted a response to early paclitaxel in combination with a platinum agent. In most cases, however, the prognosis is poor. In particular, most patients (80% in one study) with squamous cell carcinoma arising with or without endometriosis are dead of disease within only a few months of diagnosis. Based on the few published reports available, radiotherapy also seems to be of limited utility.

**COMMENT**

Although squamous elements in the ovary are relatively common, squamous cell carcinoma is distinctly rare, especially in pure form. Debate continues on the pathogenesis of primary squamous cell carcinoma without an associated dermoid. Most authors suggest squamous cell carcinoma in association with endometriosis arises from neoplastic transformation of preexisting endometrial epithelium. This may be in keeping with the varied metaplasia and neoplasia that may be seen within endometrial glands. Cases of pure primary squamous cell carcinoma of the ovary are an even greater etiologic conundrum; some authors suggest that these lesions may arise because of seeding from occult premalignant or fully malignant squamous lesions located outside the ovary. These lesions may also serve as examples of the broad potential of coelomic metaplasia.

The authors acknowledge Dean Daya, MD, MHA, FRCP, FCAP, FASCP, for his expert opinion pertaining to this review.

**References**


