Histopathologic Alterations in Ovarian Papillary Serous Cystadenocarcinomas After Neoadjuvant Chemotherapy: Possible Clinical Significance

Histopathological alterations in ovarian papillary serous cystadenocarcinoma after neoadjuvant chemotherapy and their possible clinical significance-a review

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Precis:

Histologic changes seen in ovarian serous carcinoma after neoadjuvant chemotherapy are reviewed.

Abstract:

Objectives: Neoadjuvant chemotherapy is being increasingly used prior to debulking for ovarian serous carcinoma. There can be significant histopathologic alterations, sometimes making the pathologic diagnosis challenging.

Methods: A Medline search was performed, and articles describing the histologic changes associated with neoadjuvant chemotherapy, as well as any possible clinical impact, were reviewed.

Results: The scope of histopathological changes seen after neoadjuvant chemotherapy for ovarian serous carcinoma, as well as their possible clinical significance is presented.

Conclusions: Histopathologic changes include degenerative changes, increased atypia, and alterations that may make pathologic interpretation difficult, particularly if there is a lack of familiarity with these changes and lack of available clinical history. More study is needed to assess whether there is any prognostic significance to these alterations.

Introduction:

Neoadjuvant chemotherapy is being increasingly used prior to debulking for advanced stage ovarian serous carcinoma, to permit subsequent optimal debulking. There can be significant histopathologic alterations, sometimes making the diagnosis challenging. The history of prior adjuvant chemotherapy may not be provided to the pathologist. Assessment of viability of tumor, of interest to the oncologist, can be difficult as well, and the significance is unclear. A review of the scope of histopathological changes seen after neoadjuvant chemotherapy for ovarian serous carcinoma, and their possible clinical significance is presented.

Discussion:

The mainstay for many years for initial therapy for high grade serous epithelial ovarian carcinoma is optimal debulking. Total or optimal debulking(<1 cm residual disease) is the best prognosticator of survival(1). Traditionally, debulking has been followed by chemotherapy. However, with advanced stage disease, optimal debulking at initial presentation may not be feasible, and neoadjuvant chemotherapy, where several cycles of chemotherapy are given prior to the initial surgery, may make debulking more achievable. It is now an acceptable alternative approach(2). Prior to more widespread use of adjuvant chemotherapy for cytoreduction prior to debulking, it was noted in the occasional cases that histopathologic alterations occurred that might make interpretation difficult. In a small series of serous and endometrioid ovarian carcinomas, McCluggage et al(3) noted single tumor cells or small tumor cell clusters within a fibrotic stroma. The tumor cells had undergone pronounced cytologic changes, making tumor grading and typing difficult to impossible. These included nuclear enlargement,

hyperchromatism and a smudgy appearance, as well as changes in the cytoplasm, such as eosinophilia, vacuolization, and foamy change. Background changes included fibrosis, inflammation, foamy histiocytes, cholesterol clefts , hemosiderin , calcification, necrosis, and abundant psammoma bodies(3)(figs 1,2,3). In addition to difficulties in typing and grading tumor, these authors pointed out that numerous sections, as well as immunohistochemistry may be required to establish the presence of tumor at all. Overdiagnosing clear cell carcinoma when cytoplasmic vacuolization was seen was cautioned against(3,4), with one report cautioning about the risk of diagnosing a mixed carcinoma or second carcinoma(4). Utilizing a panel of immunohistochemical stains has been suggested(5) as an aid to diagnosis, particularly helpful if a prior history of ovarian carcinoma is not available, or the cytologic changes are pronounced. Inappropriate workup and therapy may be avoided in this manner(5). Suggested stains in this panel include estrogen receptor, p53, WT1, PAX8, CK7, CK20 and CDX2. Ovarian serous carcinoma often stains for ER, P53, WT1, PAX 8, and CK7, CK 20 occasionally stains, but is more likely positive in colon cancer, which is CDX2 positive(5). The authors also suggest that diagnosis is aided in these challenging cases by good clinician-pathologist communication. In paired studies of pre- and post-chemotherapy serous carcinoma, the immunoprofile has been shown to be maintained(6). A scoring system for the histologic changes has also been proposed(2).

Recent literature has indicated that serous carcinoma of ovary and peritoneum may actually originate in the tubal fimbria. In a study by Colon et al(7), serous tubal intraepithelial carcinoma(STIC), the putative precursor lesion, was shown to persist after neoadjuvant chemotherapy, as was the p53 signature, the initial genetic aberration demonstrable by immunohistochemistry. These findings may assist in diagnosing challenging cases, particularly

if in-depth evaluation of the fimbria, such as is done in prophylactic salpingooophorectomies for BrCa mutations(SEE-FIM protocol) is conducted, which these authors recommend for neoadjuvant cases(7).

Whether or not any of the histopathologic findings seen after neoadjuvant chemotherapy signify an improved prognosis has been a topic of interest for a variety of non-ovarian solid tumors, including breast and lung(8). The literature for ovarian carcinoma is controversial. A small literature on the prognostic significance in ovarian carcinoma has evolved. In one study comparing the histology of tumor that was primarily resected versus resection after neoadjuvant chemotherapy, significant histopathologic alterations after neoadjuvant chemotherapy included single tumor cells, fibrosis, foreign body giant cells, and foamy macrophages(9), which were found to be of high specificity but low sensitivity. Less specific were inflammatory changes, hemosiderin, and psammoma bodies. Interestingly, necrosis was more highly associated with larger tumor size, and hence was more likely to occur in the controls than in the patients resected after chemotherapy in this series. Only tumor size, and no specific pathologic change correlated with longer median survival in this series, with either no tumor, tumor single cells, or tumor 5 mm or less consistent with significant response(9). The authors noted that all these regressive findings, as well as tumor giant cells, could be seen in untreated cases as well. In contradistinction, Le et al showed that lack or minimal necrosis after neoadjuvant chemotherapy was an independent risk factor for recurrent disease(10). They acknowledged the difficulty in assessing necrosis, as well as the limitations involved in a small retrospective study(10). In a subsequent retrospective study, this group(11) created a grading system that included necrosis, fibrosis, macrophages, and inflammation , and found that this composite tumor response score was prognostic for time to disease-related death. However, Ferron et al(12) found that even no

histologic residual disease did not reliably predict overall survival, although it did correlate with 3 year event-free survival, and was not a good indicator to use when planning chemotherapy after debulking.

Future and larger prospective studies will be helpful in assessing the utility of histopathologic findings after neoadjuvant chemotherapy in prognostication. One advantage to the utility of establishing histopathology of interval surgery as a prognostic factor would be that it can be available earlier than clinical markers of disease progression, including CA 125 and imaging(2). This might aid in earlier interventions, including additional chemotherapy or additional debulking procedures. In addition, the histologic findings after neoadjuvant chemotherapy can be challenging to recognize. Pathologists need to be aware of the range of histologic alterations when evaluating these specimens to arrive at the correct diagnosis. Clinician-pathologist communication is important in these difficult cases.

References:

1- Bian C, Yao K, Li L, Yi T, Zhao X. Primary debulking surgery vs. neoadjuvant chemotherapy followed by interval debulking surgery for patients with advanced ovarian cancer. Arch Gynecol Obstet. 2016 ;293:163-8.

2-Böhm S, Faruqi A, Said I, et al Chemotherapy Response Score: Development and Validation of a System to Quantify Histopathologic Response to Neoadjuvant Chemotherapy in Tubo-Ovarian High-Grade Serous Carcinoma. J Clin Oncol. 2015 ;33:2457-63.

3- McCluggage WG, Lyness RW, Atkinson RJ et al. Morphologic effects of chemotherapy on ovarian carcinoma. J Clin Pathol 2002;55:27-31.

4-Chew I, Soslow RA, Park KJ. Morphologic changes in ovarian carcinoma after adjuvant chemotherapy: report of a case showing extensive clear cell changes mimicking clear cell carcinoma. Int J Gynecol Pathol 200;28:442-6.

5-Wang Y, Wang Y, Zheng W. Cytologic changes of ovarian epithelial cancer induced by adjuvant chemotherapy. Int J Clin Exp Pathol 2013;6:2121-8.

6-Miller K, Price JH, Dobbs SP, McClelland RH, Kennedy K, McCluggage WG. An immunohistochemical and morphological analysis of post-chemotherapy ovarian carcinoma. J Clin Pathol. 2008;61:652-7.

7-Colon E, Carlson JW. Evaluation of the Fallopian Tubes after neoadjuvant chemotherapy: persistence of serous tubal intraepithelial carcinoma. Int J Gynecol Pathol 2014;33:463-9.

8-Sethi D, Sen R, Parshad S, Khetarpal S, Garg M, Sen J. Histopathologic changes following neoadjuvant chemotherapy in various malignancies. Int J Appl Basic Med Res 2012;2:111-16.

9-Sassen S, Schmalfeldt B, Avril Net al. Histopathologic assessment of tumor regression after neoadjuvant chemotherapy in advanced-stage ovarian cancer. Hum Pathol 2007;38:926-34.

10-Le T, Shahriari P, Hopkins L, Faught W, Fung M. Prognostic significance of tumor necrosis in ovarian cancer patients treated with neoadjuvant chemotherapy and interval surgical debulking. Int J Gynecol Cancer 2006;16:986-90.

11-Le T, Williams K, Senterman M, Hopkins, L, Faught W, Fung M. Histopathologic assessment of chemotherapy effects in epithelial ovarian cancer patients treated with neoadjuvant chemotherapy and delayed primary surgical debulking. Gynecol Oncol 2007;106:160-3.

12-Ferron J, Uzan C, Rey A et al. Histologic response is not a prognostic factor after neoadjuvant chemotherapy in advanced stage ovarian cancer with no residual disease. Eur J Obstet Gynecol Reprod Biol 2009;147:101-5.