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Immunohistochemical c-kit expression in uterine serous carcinoma tissue

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Summary

Aim: Uterine serous carcinoma (USC) is an aggressive tumor that represents only 10% of endometrial cancer cases but accounts for a disproportionate number of deaths due to uterine cancer. Advances in the development of specific c-kit receptor-targeted drugs have promoted its potential therapeutic application as a target in tumor-related diseases. The aim of the present study was to evaluate imunohistochemical expression of c-kit in USC tissue in order to assess whether positive cases can be candidates for targeted therapy. *Materials and Methods:* C-kit expression assessment by immunohistochemistry was performed on deparaffinized sections of paraffin-embedded tissue blocks of confirmed consecutive available USC uterine specimens of patients diagnosed from 2000 to 2014. Sections of gastrointestinal stromal tumor (GIST) tissue known to contain c-kit served as positive controls. *Results:* Immunohistochemical c-kit staining was not observed in any of 31 USC tissue samples examined. Intense staining was observed in the sections of GIST tissue. *Conclusion:* The present results may indicate that primary USC is not a candidate for c-kit targeted therapy.

Key words: C-kit tissue expression; Uterine serous carcinoma; Targeted therapy.

Introduction

Uterine serous carcinoma (USC) represents only 10% of endometrial cancer cases. It has a poor prognosis and accounts for a disproportionate number of deaths due to uterine cancer. While endometrioid carcinoma is diagnosed in an advanced stage in only about 20% of cases, USC is diagnosed in advanced stages in about 40% of the cases. Even in apparent clinical early-stage disease, USC is found to have unfavorable pathological prognostic factors such as lymphovascular space invasion, lymph node involvement, and microscopic intraperitoneal spread [1, 2].

The c-kit receptor is an important member of the tyrosine kinase family that regulates cell differentiation and proliferation, resists cell apoptosis, and plays a major role in tumor occurrence, development, migration, and recurrence through interaction with the stem cell factor [3]. Advances in the development of specific c-kit receptor-targeted drugs have promoted its potential therapeutic application as a target in tumor-related diseases [4]. Data with regard to c-kit expression in USC tissue are very scarce and contradictory [5,6].

The aim of the present study was to examine immunohistochemical expression of c-kit in USC tissue in order to assess whether positive cases can be candidates for targeted therapy.

Material and Methods

Paraffin-embedded tissue blocks of consecutive available uterine specimens of USC patients diagnosed from 2000 to 2014 were examined after institutional review board approval. Formalin-fixed hematoxylin-eosin stained six-µm slides from the tissue of the same cases were newly performed and reviewed by an expert pathologist (LS) in order to verify the diagnosis. The records of the study group patients were retrospectively abstracted and their clinicopathological data were recorded.

Immunohistochemistry was performed on deparaffinized four-µm sections of paraffin-embedded tissue blocks, on a staining system. The detection of CD117/ c-KIT was done using rabbit polyclonal antibody diluted to 1:500, and a biotin free, multimer technology based on Ultra View Universal DAB detection system. Sections of gastrointestinal stromal tumor (GIST) tissue known to express c-kit served as positive controls.

Results

The study comprised uterine tissue samples of 31 USC patients**.** The mean age of the patients at diagnosis was 74 years (range 57-84). Post menopausal bleeding was the presenting symptom in 29 (78.4%) patients. Only 14 (37.8%) patients were diagnosed in Stage I and the remaining 23 (62.2%) in Stages II-IV. Treatment consisted of surgery followed by platinum-based combination chemotherapy ± radiotherapy in 29 (78.4%) patients and surgery alone in seven (18.9%) patients. One patient (2.7%) refused treatment. Positive immunohistochemical c-kit staining was not

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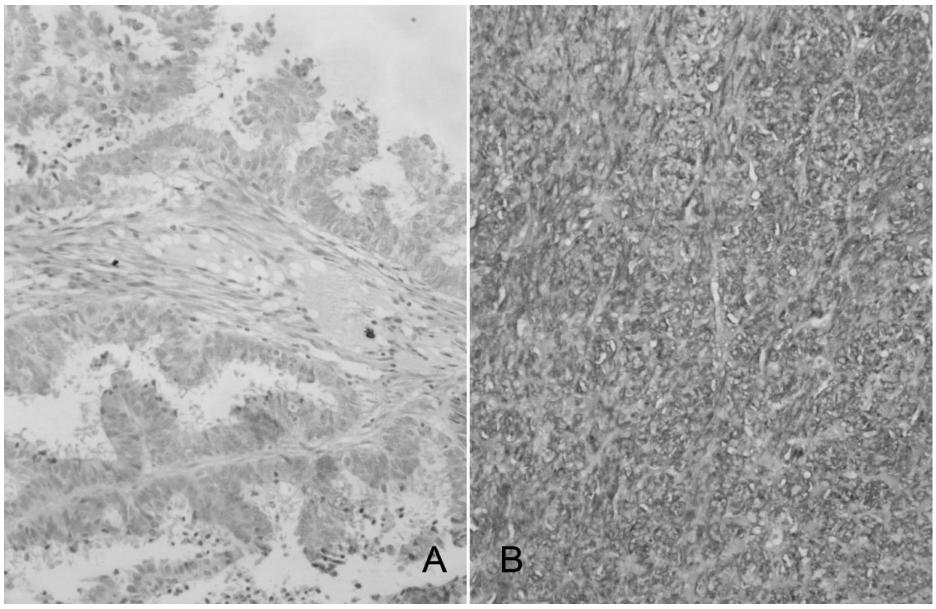

Figure 1. — Immunohistochemical c-kit staining staining of uterine serous carcinoma and GIST. A) Uterine serous carcinoma - no c-kit staining. B) GIST - intense c-kit staining.

observed in any of the USC tissue samples examined. Intense staining was observed in the sections of GIST tissue (Figure 1).

Discussion

We found that none of the 31 USC uterine specimens immunohistochemically stained for c-kit. They are aware of the small number of USC specimens in our study. However the rarity of this type of endometrial cancer should be taken in consideration.

Through a PubMed search, we could locate only two previous studies of endometrial carcinoma in which immunohistochemical c-kit expression in a very limited number of USC specimens was mentioned. In one study of 72 endometrial carcinomas, eight of ten USCs were c-kit positive [5]. Diffuse staining and intense staining was observed each in only two USC specimens.

In contrast, in the other study of endometrial carcinoma [6], c-kit expression was not seen in any of the 33 primary endometrial endometrioid or in the 11 USC carcinomas. And yet, two of eight (25%) of the recurrent endometrioid cancers and two of four (50%) of the recurrent USC cancers did express c-kit. The authors concluded that the results of their study support the initiation of a clinical trial using imatinib mesylate for the treatment of advanced or recurrent endometrial cancer. Regretfully data regarding c-kit expression in specimens of recurrent USC in the present patients are unavailable.

The reason for the discordant results in these studies is obscure. The present results are in accordance with those of Slomovitz *et al.* [6] namely that c-kit is not present in the tissue of primary USC. These results may be taken to indicate that primary USC is not a candidate for c-kit targeted therapy. Nevertheless, further studies of c-kit expression in larger series of USC in order to elucidate these issues and to settle the contradictory results with regard to its frequency of expression and its prognostic and therapeutic value are warranted.

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