Primary melanomas of the anus and rectum are rare neoplasms with aggressive behavior, accounting for 0.1%-4.6% of anal canal tumors. Mucosal melanomas account for approximately 1.2% of all melanomas, of which fewer than 25% are anorectal. Histological evaluation with immunohistochemical stains like HMB-45, S-100, vimentin and Melan A is required for definitive diagnosis. The 5-year survival rate for anorectal melanomas (AM) was reported to be as low as < 20%, in contrast to the value of approximately 80% for cutaneous melanomas. Furthermore, up to 67% of patients are found to have distant metastases at the time of their initial diagnosis with AM. Since the chemotherapy treatment possibilities are limited, patients usually undergo mutation detection tests giving the opportunity of targeted therapy. Herein we report a case of a patient with anorectal melanoma, diagnosed in stage II and the pathomorphological and mutation status finding, together with their correlation to tumor behavior and patient prognosis.

INTRODUCTION

Melanomas are malignant mesenchymal tumors originating from melanocytes. The primary location of origin is most often in the skin, eyes, mucosal surfaces of the head and neck area, anorectum, genitalia etc. Ultraviolet B radiation is the number one risk factor for the development of melanoma. However, the anal mucosa is not an area exposed to sunlight and an underlining trigger for the development of anal melanoma is still widely unidentified.

Primary melanomas of the anus and rectum are rare neoplasms with aggressive behavior, accounting for 0.1%-4.6% of anal canal tumors and less than 2% of all melanomas. A sampling of cancer registries in U.S. cities revealed an incidence of 1.7 cases per 1 million per year. The median age at which the condition is diagnosed is 55 years, although ranging from 29 to 91 years of age. Certain areas of the world, such as Australia and New Zealand have a higher predominance of the condition. Primary symptoms reported include bleeding, anal pain, palpable anal mass, anal pruritus, tenesmus, and change in bowel habits. If a metastatic disease is present, symptoms may also include medium to severe weight loss, anemia, generalized fatigue, groin masses, pelvic masses, or even bowel obstruction.

The diagnosis is often delayed, which combined with aggressive nature of the malignancy, leads to patients with anal melanoma frequently to be...
Figure 1. Anorectal melanoma. 1a - submucosal growing pigment lesion, H&E, original magnification 10x. 1b - high magnification of the tissue biopsy showing enlarged polymorphous cells with large vesicular nuclei, irregular nuclear borders, condensed chromatin, and numerous atypical mitoses; dark-brown pigment clusters between the cells, H&E, magnification 200x. 1c - neoplastic proliferation of cells under the mucosal layer, H&E 80x.
Figure 2. Anorectal melanoma. Immunohistochemistry of biopsy tissue - identical slide location on all sections. 2a - HMB-45 positive reaction, original magnification 40x. Melan-A positive reaction, original magnification 40x. 2c - vimentin positive reaction, original magnification 40x. 2d - S100 positive reaction, original magnification 40x.

Figure 3. Anorectal melanoma. Immunohistochemistry with diffusely positive reaction for CD117. 3a - diffusely positive reaction, original magnification 10x. 3b - CD117 positive cytoplasm and membrane reaction, original magnification 400x.
between them (Fig. 1b). Focal necroses were present, together with perirectal and perianal adipose tissue invasion, which combined with the size of the tumor gave reason to assess the condition as stage II.

Additional immunohistochemistry staining with HMB45, Melan A, S100 protein, vimentin, and CD3 were performed, all of which showed a strong positive reaction, confirming the diagnosis (Fig. 2). A strong positive reaction with CD 117 in more than 80% of the melanoma cells was also present (Fig. 3). A Cobas 4800 Real-time PCR test for a BRAF V600E mutation detection was also performed to a negative result. The additional staining for Ki-67, a cellular marker for proliferation, showed high intensity in more than 40% of the cells, certifying the malignant nature of the tumor.

DISCUSSION

Anorectal melanomas often are diagnosed late in their pathobiological development, resulting in poor prognosis. There is a tendency for alternative therapy application, often depending on the results of the mutational status of the tumor.

Taken together with their extreme rarity, 1.7 cases per one million, the diagnosis is extremely difficult based on clinical presentation alone, the clinical presentation can more often than not be mistaken for colorectal cancer, leading to delay or inadequate treatment or surgical procedures being undertaken. Earlier symptoms of the tumor such as pseudoconstipation, feeling of a tender mass during defecation can also be mistaken for other conditions.

Therefore in most cases the condition is already severely advanced and diagnosed in stage IV. Due to these facts however, the true incidence of anorectal melanoma may be significantly higher as place of origin of metastatic melanoma, without unknown primary location, which in different populations based on statistical reports varies from 5 to 20%.11,12

Regardless of all factors in the epidemiology of anorectal melanoma, the pathogenesis of this distinct clinical entry varies severely from skin melanoma, due to the lack of several predisposing factors in the area. This baffling pathogenesis is also evident from the presence of several mutations, which vary significantly from those observed in skin melanoma.10

KIT mutations are most commonly detected in acral melanomas with 23% and in mucosal melanomas with 15.6%. They are seldom found in melanomas with other locations such as conjunctival, with 7.7% and cutaneous, with 1.7%. KIT copy number was also most commonly detected in acral, with 27% and mucosal melanomas, with 26%.14-16

There is also a strong correlation with KIT gene alterations are immunoreactivity with CD117, thus an emphasis should be put on the CD117 status.13-15 Thus a routine application of CD117 immunohistochemistry in pathological diagnosis is indicative with a predictive purpose.7,13

BRAF V600E mutations are reportedly identified in 26.7% of conjunctival melanomas and 55.7% of cutaneous melanomas, but only in 1.1% of the mucosal melanomas.17

The CD3, in this case, recognized most of the tumor-infiltrating lymphocytes (TIL). There were a large number of TIL in the tumor sample forming multiple groups throughout. Furthermore TIL, as in this case, often correlate with the positive mutational status of the melanoma.18

CONCLUSION

Anorectal melanoma is an aggressive and rare malignancy, often presenting clinically late in its pathobiological behavior, with five-year survival rate ranging from 3 to 22% and further survival in patients with recurrent or metastatic disease being less than 10 months.7 There are currently no reported cases in the literature of long-term survivors, where metastatic disease is present.

Chemotherapy and targeted chemotherapy, radiation therapy, or both, in addition to surgery, are likely to provide the best available treatment options for metastatic disease in advanced anorectal melanoma.7

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Аноректальная меланома - гистопатологический клинический случай и литературный обзор

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Дата получения: 29 марта 2018
Дата приемки: 22 мая 2018
Дата онлайн публикации: 06 августа 2018
Дата публикации: 29 ноября 2018

Ключевые слова: аноректальная меланома, меланома, KIT, CD117, BRAF V600E

Первичная меланома заднего прохода и прямой кишки является редким новообразованием с агрессивным поведением и составляет 0,1% - 4,6% случаев рака анального канала. Слизистые меланомы составляют примерно 1,2% всех меланом, из которых менее 25% являются аноректальными. Необходима гистологическая оценка с применением иммуногистохимических растворов, таких как НМВ-45, S-100, виментин и Мелан А для окончательного диагноза. О пятилетней выживаемости в случаях аноректальных меланом (AM) сообщается менее чем в 20% случаев, в отличие от показателей в 80% для кожных меланом. Кроме того при 67% пациентов обнаруживаются отдалённые метастазы во время первоначального диагноза с AM. Поскольку возможность химиотерапии ограничена, пациенты обычно проходят тесты на мутацию, что позволяет проводить целенаправленную терапию. Настоящий клинический случай касается пациента с аноректальной меланомой, с диагнозом II стадии и с находками патоморфологического и мутационного статуса, наряду с их корреляцией с поведением опухоли и прогнозом для пациента.