Malignant melanoma metastasis in the gallbladder. A case report of an unusual metastatic site

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ARTICLE INFO

Article history:
Received 27 August 2020
Received in revised form 16 September 2020
Accepted 16 September 2020
Available online 19 September 2020

Keywords:
Malignant melanoma
Gallbladder metastasis
Cholecystectomy
Immunotherapy
Case report

ABSTRACT

INTRODUCTION: Malignant melanoma is a neoplasia with the ability to metastasize to all organs. Most frequently, metastases derives from a skin primary. A solitary metastasis in the gallbladder is rarely mentioned in current literature.

PRESENTATION OF CASE: We present the case of a 62-year-old female patient with the unusual metastatic spread of malignant melanoma into the gallbladder. The lesion was detected during routine follow-up appointment six years after the initial surgical and radio-chemotherapeutic treatment of a malignant melanoma on the back. Following multidisciplinary team meeting, it was decided to perform a laparoscopic cholecystectomy to remove the gallbladder metastasis.

DISCUSSION: New occurrence of a melanoma metastasis in the gallbladder is extremely rare, especially in stable disease. The therapeutical concept must be discussed extensively in the present of this metastasized tumor.

CONCLUSION: In otherwise stable disease, palliative surgery for metastasis in the gallbladder is a possible option to prevent biliary complications. In a palliative setting always weigh up the risks and benefits while maintaining the quality of life.

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1. Introduction

Malignant melanoma is one of the five most common types of cancer. It accounts for 4–7% of all new cancer cases and 1.5% of all cancer deaths [1]. Beside the skin, primary malignant melanoma can be found in mucous membranes, such as the lung, genitourinary or gastrointestinal tract, representing 1.3% of all melanomas [2]. In the metastatic setting, a distinction is made between locoregional metastasis in the surrounding tissue and lymph nodes (stage IIIA–D) and distant metastasis (stage IV) [3]. Traditionally, prognosis of metastatic melanoma was very poor with 10-year overall survival (OS) rate of less than 10% [4]. Single-agent chemotherapy is associated with response rates of only 5–20% [5,6]. Early approaches with the use of immunotherapeutic agents such as high-dose interleukin-2 were associated with durable responses in a small percentage of patients but with substantial toxicity [7]. Over the past 10 years, increased biological understanding and access to innovative therapeutic substances have transformed advanced melanoma into a new oncological model for treating solid cancers. Treatments that target B-Raf proto-oncogene serine/threonine-kinase (BRAF) V600 (Val600) mutations using selected BRAF inhibitors combined with mitogen-activated protein kinase inhibitors (MEK inhibitors) have significantly improved response and OS. Furthermore, advanced cutaneous melanoma has developed into a prototype for testing checkpoint-modulating agents [8]. 5-year OS-rates for metastatic melanoma have increased substantially from less than 10% to up to 40–50% today in countries that have access to these innovations [9].

Regional lymph nodes, lung and brain are the most frequent metastatic sites, involvement of the gastrointestinal system is rare with 2–4%, mostly in the small intestine, colon and stomach [10,11]. Gallbladder metastases is mainly an incidental findings in autopsies and rarely described in living patients due to poor prognosis with
a mean survival rate of 8.4 months [11–13]. The main therapeutic
goal in these patients is the prevention of complications such as
cholecystitis, icterus and the obstruction of the common bile duct,
a haemobilia and biliary fistulas [14]. However, in a scenario of an
isolated gallbladder metastasis, one year survival-rate is 100% [15].
In this case report, we intend to describe the nature of the disease,
outline therapeutic options and raise awareness of the importance
of follow-up in these patients. This case report has been reported
in line with the SCARE criteria [16].

2. Case

A 62-year-old patient with initial right sided paravertebral
malignant melanoma. The slowly growing skin lesion was biopsied
in July 2013. The findings showed a malignant melanoma Bres-
low 1.3 mm, stage II A (pT2b pN0 sn 0/2) cM0. A second resection
with a safety margin of 0.5 cm was done. In February 2016, a fur-
ther excision of a 6.5 mm (resection margin 0.1 mm) cutaneous
lesion in the right flank was performed. Histological examination
arised metastatic progression and a resection with a 0.5 cm margin
was carried out. Next gene sequencing analysis of the meta-
ysis revealed mutations in BRAFp.V600E. Further staging with Positron Emission Tomography (PET)/computed tomography (CT)
revealed several cutaneous and subcutaneous masses with hyper-
metabolism and multiple lung metastases. Immunotherapy with
the anti-PD-1 antibody pembrolizumab was initiated. After three
months of therapy, CT scan in July 2016 showed a good partial
remission. The patient suffered various immune-mediated toxic-
ities, including grade 3 skin exanthema and elevation of creatinine
kinase without evidence of myocarditis. The macular exanthema
was biopsied and revealed an indicated Graft versus Host Disease-
like lichenoid dermatitis with focal destruction of the basal cell
series, dyskeratosis, discrete pigment incontinence and perivascu-
lar lymphocytosis, well compatible with checkpoint inhibitor side
effects. The patient also had pronounced vitiligo. Due to severe side
effects, pembrolizumab was discontinued after 3 months. Toxiciti-
ties were treated with oral corticosteroids for 2 months. After this
period, a re-exposure with pembrolizumab was attempted, which
led to a renewed massive flare-up of skin toxicity. Therefore pem-
brolizumab was permanently suspended. A growing metastasis on
the left dorsal lower leg was irradiated with a total of 30 Gy in
December 2016. Repeated CT and Magnet Resonance Tomography
scans showed size-constant pulmonary metastases with central
calcifications, suggesting stable pulmonary disease for three years.
In September 2018 a CT scan revealed a new lesion in the gall-
bladder wall adjacent to a hypervascularized liver lesion, highly
suspicous of a further metastatic deposit. A biopsy of the hepatic
lesion showed no sign of malignancy, however the gallbladder
lesion emerged to be a metastasis of an amelanotic melanoma. Due
to this disease progression, a new therapy with pembrolizumab
was again initiated. This time the patient initially tolerated the
therapy without relevant side effects. Radiologically treated
lesions led to a stable disease. Following extensive discussion at our
multidisciplinary team meeting (MDT), elective laparoscopic chole-
cystectomy was recommended on the base of otherwise stable
disease over years. Intraoperatively, there was an inconspicuous
situs without signs of peritoneal carcinomatosis. Macroscopically,
a slight discoloration was seen on the anterior surface of the gall-
bladder, which revealed itself as a 1 cm intravesical tumor nodule
on palpation (Fig. 1). Histopathology confirmed a largely amelan-
otic, partly spindle cell, partly epithelioid cell, predominantly vital
metastasis. The immunohistochemical study showed PD-L1 (SP263

Fig. 1. CT abdomen (portal venous phase) transversal plane (A), coronal plane (B) and macroscopic finding (C) with gallbladder (red) and metastasis (blue).
Ventana) positivity. Membrane staining in tumor cells and tumor-associated mononuclear immune cells corresponded to a MEL score 2 (5%) according to Daud et al. (Fig. 2A–D) [17]. Due to the renewed flare-up of the skin exanthem immediately prior to the planned surgery, another short-term therapy with prednisone was necessary. After discontinuation of the corticosteroid, the skin reaction flared up briefly. Postoperatively, it was therefore decided not to continue the therapy with pembrolizumab for the time being. The radiological follow-up showed an unchanged partial remission of the pulmonary metastases. At present, 15 months after resection of the gallbladder, the patient is in very good general condition without indications of a new tumor progression.

3. Discussion

Metastatic spread of a malignant melanoma into the gallbladder is a rare event, described only in individual cases. The newly emerging gallbladder lesion appears unusual since the other metastases responded well to immunotherapy. Since, the reason of the delay in the initial surgical management cannot be clearly identified, the main topic in this case, is whether surgery should be performed in this widespread metastatic situation. The decision of performing the operation was based on the fact of an otherwise stable disease over years, supported by a case report of Gogas et al. [13]. Alternatively, surgery could have been withheld until biliary complication occurred. Possible alternatives would have been antibiotics, biliary stenting or cholecystostomy. With regards to surgical access we decided to perform a minimal invasive technique. Due to the size and clearly localized lesion on imaging, a laparoscopic procedure was possible. The open technique would be safer with respect to tumor spread in the port canal, but associated with higher morbidity [12,18].

The specimen was analyzed histopathologically and immunohistochemically. The examination of tumor cells revealed membrane-positive expression of PD-L1 in 5% of tumor cells and tumor-associated mononuclear immune cells. Melanomas with more than 1% PD-L1 positive tumor cells and tumor-associated immune cells are more likely to respond to immunotherapy than PD-L1 negative tumors [17]. Although PD-L1 expression is not regarded as a relevant predictive tumor marker, from an oncological perspective, further therapy with pembrolizumab was recommended. Alternatively, a combined BRAF and MEK inhibition, would have been a possible approach in this clinical stage. Since combination show a higher response rate and longer survival rate as compared to BRAF inhibition alone (Dabrafenib and Trametinib, Encorafenib and Binimetinib and Vemurafenib plus Cobimetinib) [19–21]. Of note, the patient initially had a melanotic melanoma, but the resected metastasis in the gallbladder showed an amelanotic melanoma. A dedifferentiation of the initial tumor not responding to immunotherapy is a possible explanation. In

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1. Hematoxylin and Eosin staining.
2. CD8 staining.
summary the therapeutic concept and management of patients with widespread metastatic melanoma needs an interdisciplinary discussion in a MDT, properly balancing risk and benefits with quality of life in these palliative situations.

4. Conclusion

Diagnosis of gallbladder metastasis in malignant melanoma is difficult due to its rarity and absence of symptoms. However, complications can be life limiting. Management can be surgical or medical, but discussion and definition of a major treatment plan need to be addressed in MDT meetings. The laparoscopic cholecystectomy can avoid biliary complications in a palliative setting.

Declaration of Competing Interest

There are no conflict of interests regarding this article.

Funding

There are no sources of funding regarding this article.

Ethical approval

On the basis of this being a case report and with a present handwritten signed consent of the patient, this case report is exempt from ethical approval.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

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- Prof. Dr. med Katharina Glatz: Image preparation, histological analysis, proofreading.
- PD Dr. med. et Dr. phil. Sacha I. Rothschild: History workup, analysis of the oncological therapies, proofreading.
- Prof. Dr. med. Otto Kollmar: Proofreading.
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Registration of research studies

N/A.

Guarantor

Dr. med. Gabriel Fridolin Hess.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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