case report

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The path of an esophageal carcinoma patient from curative to palliative treatment

Ercan Müldür · Karl Mayrhofer · Wolfgang Hilbe

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Summary We hereby report the course and management of a patient with human epidermal growth factor receptor 2 negative esophageal cancer who received neoadjuvant chemoradiation, surgical resection and subsequently palliative therapy for recurrent disease. The critical role of the staging procedure is discussed. Additionally the options of systemic palliative therapies are presented and the rationale for immuno-oncologic treatment is highlighted. The patient received pembrolizumab as second-line therapy, which unfortunately did not result in a response and caused minor autoimmune side effects.

Keywords CROSS protocol · Ivor Lewis esophagectomy · Pembrolizumab · Immunotherapy · FLOT protocol

Case

We report on a 72-year-old male patient with an adenocarcinoma of the esophagogastric junction, moderately differentiated, intestinal type with initial diagnosis in March 2016.

The patient was admitted as an inpatient to our department for further clarification due to recent presentation of clinical symptoms like nausea and vomiting, difficulties in swallowing, as well as chest pain. An initially performed gastroscopy suggested a tumor of the esophagogastral junction. Computed tomography of the thorax and abdomen showed an extensive, irregular, stenotic, eccentric wall thickening at the gastroesophageal junction corresponding to the observed gastric malignancy (Fig. 1). Dimensions were approximately 6.0 × 4.6 × 3.3 cm. Multiple pathological perigastric lymph nodes around the cardia and around the most distal esophagus were found. Two small hypodense liver lesions of 6 mm in segment IVA and VIII, primarily compatible with cysts, which could not be further evaluated due to their small size, were also noticed. At stage III according to Union for International Cancer Control (UICC), preoperative concomitant radiochemotherapy with carboplatin and paclitaxel according to the CROSS protocol was initialized after a tumor board decision [1]. The patient received treatment from March to May 2016. Subsequently, on July 14, 2016, Ivor Lewis esophagectomy was performed [2].

Postoperatively, the tumor was histologically staged ypT3 ypN1 (1/30) M0, no lymphovascular invasion (LVI), no expression of human epidermal growth factor receptor 2, programmed death ligand 1 (PD-L1) negative and no microsatellite instability. Both surgery and postoperative course were free of complications. Regular follow-up visits and computed tomographies were performed at our outpatient clinic; no further adjuvant treatment was given according to current guidelines.

In June 2017, unfortunately, a lymphatic node relapse as well as peritoneal carcinomatosis was diagnosed. Having a patient in very good performance status of Eastern Cooperative Oncology Group (ECOG) 0 in a now metastatic setting, we opted for the maximum treatment strategy and the patient underwent polychemotherapy consisting of fluorouracil, oxaliplatin and docetaxel according to the FLOT protocol [3]. The patient received four cycles of this therapy resulting in a partial remission of the tumor. Due to treatment-related diarrhea, recurrent infections and at the patient's request, chemotherapy was discontinued afterwards.

E. Müldür, MD (✉) · K. Mayrhofer · W. Hilbe
Department of Medical Oncology, Hematology and Palliative Care, Wilhelminenspital, Montlearstraße 37, 1160 Vienna, Austria
ercan.muelduer@wienkav.at

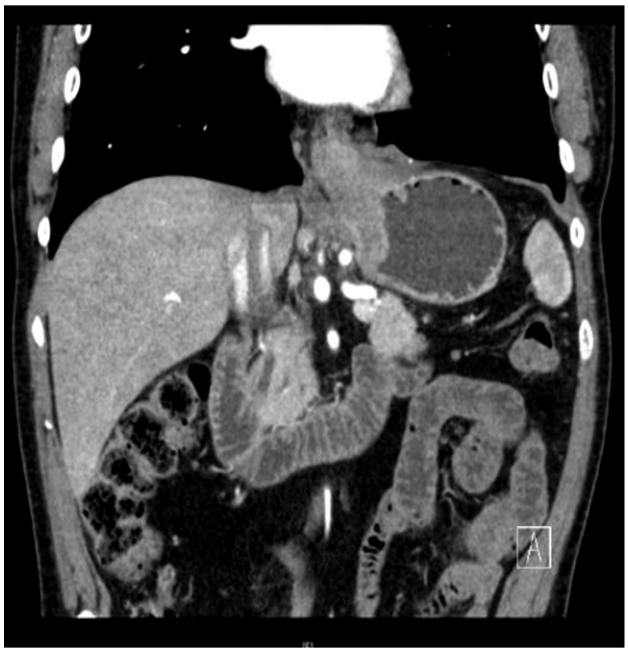

Fig. 1 Carcinoma of the gastroesophageal transition

In the further course, regular clinical and radiological progress checks were carried out every 2 to 3 months. In February 2018 pulmonary metastases were diagnosed. Based on the low tolerability of the previous chemotherapy the decision for immunotherapy with administration of pembrolizumab based on the results of the Keynote-059 study was made by our tumor board [4]. Three months after the start of pembrolizumab therapy, restaging revealed tumor progression with an increase in peritoneal carcinomatosis and a new metastasis in the right kidney; additionally, subclinical pneumonitis (Fig. 2b) and cholecystitis (Fig. 2a) were detected [5]. Aforementioned immune-related adverse effects, pneumonitis and cholangitis, were easily controlled by immunosuppression via oral corticosteroids [6].

Due to the now reduced general condition of the patient with ECOG III, a "best supportive care" concept was chosen for the further clinical course. Currently, the patient is under good palliation.

Discussion

Several retrospective analyses as a well as a recently published meta-analysis showed increased disease-free and overall survival rates in patients achieving complete pathologic remission after neoadjuvant therapy [7–9]. In our patient, this was not the case; still, neoadjuvant treatment was effective leading to a histologic regression with subsequent R0 resection. Ivor Lewis esophagectomy is an extensive surgery which yields a significant rate of postoperative morbidity and mortality; however, our patient recovered quite well without any complications.

Especially for a curative treatment strategy, exact staging is essential. Computed tomography combined with endoscopic ultrasound might still lead to a understaging as shown by several studies evaluating the use of positron emission tomography (PET) for potentially resectable tumors [10]. Up to 20% of patients are upstaged when using PET scans preoperatively resulting in a change of the management [11]. Additionally, even tumors deemed resectable by PET scan can have inoperable disease upon surgical exploration. However, routine use of PET in all patients is not advocated by current guidelines, possible selection criteria include locally advanced disease shown by routinely used imaging methods as this probably increases the chance of metastatic disease.

Published data suggest that more than half of all patients undergoing curative resection experience recurrent disease during follow-up, as this was the case in our patient 15 months after initial diagnosis. He then received chemotherapy according to the FLOT protocol which represents the current standard of care for human epidermal growth factor receptor 2 negative disease [3]. Due to substantial toxicities despite

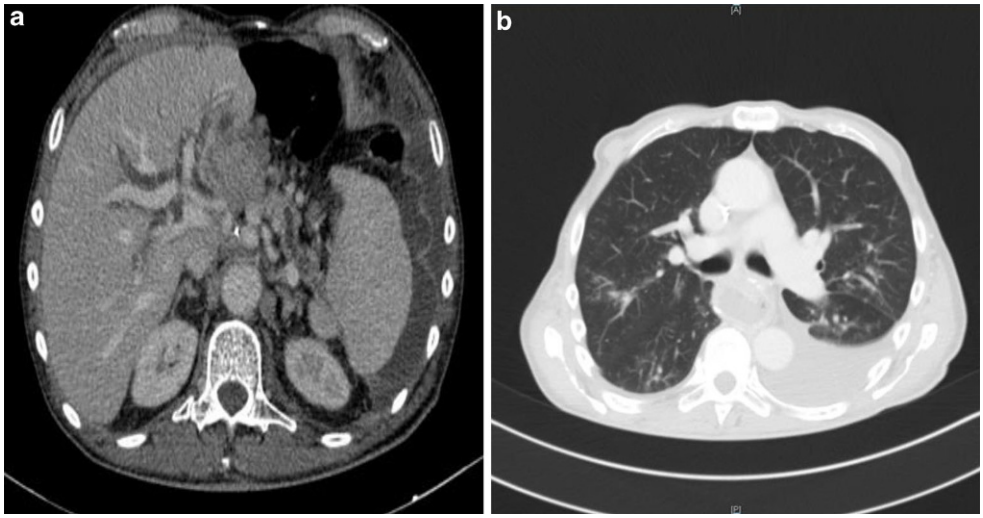

Fig. 2 **a** Pembrolizumab-induced cholangitis, **b** pembrolizumab-induced pneumonitis

a proven chemosensitivity resulting in a very good response, therapy was stopped after the fourth cycle. In the absence of substantial toxicities and disease progression, we would usually continue treatment for a total of 12 cycles.

When progressive disease was confirmed in February 2018, well-established treatment options included irinotecan or ramucirumab [12]. Nevertheless, due to encouraging results of the phase 2 Keynote-059 trial, pembrolizumab was administered [4]. In June 2018, results of the phase 3 Keynote-061 trial comparing pembrolizumab with paclitaxel in PD-L1 positive tumors were published, showing no clinical benefit for immunotherapy versus paclitaxel [13]. However, there are patients with long-lasting remission due to immunotherapy. A possible biomarker for identification of these patients could be the microsatellite instability status as shown by several small basket trials including a variety of solid tumors—as well as esophageal cancer—with promising results of anti-PD-1 therapy [14, 15].

This case report represents the typical disease course and management of a patient with esophagogastric junction carcinoma highlighting the need for improvements in treatment of both locally and advanced disease.

Conflict of interest E. Müldür, K. Mayrhofer, and W. Hilbe declare that they have no competing interests.

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