Surgical treatment of metastatic VIPoma: a case report

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***Abstract*:** VIPoma, a neuroendocrine tumour mostly occurring in the human pancreas and producing high levels of vasoactive intestinal peptide, is a rare disease that presents with a wide spectrum of symptoms, including intense diarrhoea, hypokalaemia, and cardiac complications, with life-threatening consequences. In most cases, metastatic lesions are present at VIPoma diagnosis. Treatment options include symptomatic therapy, chemotherapy, radiation and surgery. Due to its low incidence, there are no evidence-based therapy recommendations to date. Here, we present a case of a 39-year-old woman with severe symptoms due to VIPoma of the pancreas with diffuse hepatic metastasis, who underwent simultaneous resection of the primary tumour, extensive liver resection and radiofrequency ablation. The patient was released in good health and was recurrence-free during 12 months surveillance. According to the existing literature and our own experience, surgical procedures appear to be the most promising therapy option for cases with diffuse hepatic metastasis, offering patients relief from their symptoms and (chemo)therapy-free time.

Keywords: case report, metastatic VIPoma, surgery

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Introduction

Vasoactive intestinal peptide (VIP) is a gastrointestinal peptide, discovered by Gardner and Cerda[1] with a variety of functions, including gastrointestinal, vaso-cardial and neuronal effects. In addition, VIP affects the respiratory system, growth and carcinogenesis, and the immune system.[2]

Due to the multiple effects of VIP, deregulated high levels of the peptide in the blood result in a spectrum of severe symptoms. Such severe symptoms are found in patients with VIPoma, a neuroendocrine tumour (NET) mostly occurring in the human pancreas producing high levels of VIP. This disease is also called *Verner-Morrison syndrome* after its discoverer Verner and Morrison[3] or *WDHA* as an acronym for its main symptoms (water diarrhoea hypokalaemia achlorhydria). It is a very rare disease with an incidence rate of 1 case per 10,000,000 person-years.

In most cases, patients with VIPoma already show metastatic lesions at diagnosis. Treatment options include symptomatic therapy, chemotherapy, radiation and surgery. At present, many clinicians are reluctant to choose surgical approaches for metastatic VIPoma, even though these patients have serious and even life-threatening symptoms, and despite all efforts, the effect of conservative methods is often limited.

Here, we present a case of a 39-year-old woman with life-threatening symptoms due to metastatic VIPoma. We obtained a signed consent of the patient for publishing the data and de-identified the data as far as possible. An ethics approval was not necessary for this case report.

Methods

The present case report is designed after the CARE case report guidelines. The CARE guidelines (for

CAse REports) were developed by a group of experts to increase in the accuracy, transparency, and usefulness of case reports[4]. The CARE checklist of information to include when writing a case report is added as Supplementary File.

A case report

In April 2019, a 39-year-old woman presented with therapy-resistant VIPoma of the pancreatic tail with multiple (>10) hepatic metastasis in an impaired general state of health. The patient's height was 170 cm and her weight 60 kg. Beside from VIPoma the patient's medical history included a performed hysterectomy in 2018 because of myoma and an eradication therapy of helicobacter pylori also in 2018. There were no relevant family history or genetic information. Hepatic staetosis and pollen allergy were the only concomitant diseases. The physical examination showed a lightly elevated heart rate (110/min), sinus rhythm, normal respiratory sounds, abdomen and extremities showed no pathological findings. The patient reported about four admissions to intensive care unit (ICU) between January and April 2019.

First diagnosed in 2017, the patient had accelerating diarrhoea (6–7 stools/d) and hypokalaemia, despite all diet and therapy efforts. The episodes were extraordinarily severe. On multiple occasions, the patient needed treatment in the ICU due to strongly dysregulated electrolytes, hypovolaemia and metabolic acidosis. She had visited different major German hospitals for consultation. Different treatments were applied: initial electrolyte adjustment and octreotide therapy and later lanreotide therapy followed by chemotherapy with capecitabine and temozolomide. Due to the advanced metastatic stage, a surgical procedure had not yet been recommended.

At the time she came for consultation at the University Medical Center Goettingen, the tumour in the pancreas tail was approximately 2 cm in diameter. The liver showed multiple (>10) metastases distributed in all segments. Magnetic resonance imaging (MRI) scans showing the extent of the liver metastasis are presented in Figure 1(a).

A histopathological work-up from the biopsy showed a classic neuroendocrine tumour with 10% proliferation rate (Ki67 index), resulting in a tumour grade G2 according to European Neuroendocrine Tumor Society (ENETS) criteria.[5]

The initial level of serum VIP, as measured in January 2019, was 334 pmol/l (normal values: <30 pmol/l). Positron Emission Tomography- Computed Tomography (DOTATATE-PET-CT) from February 2019, the pancreatic tail tumour and liver lesions were positive for somatostatin-2 receptors. Due to an asymptomatic pulmonary embolism revealed by PET-CT, the patient was started on treatment with 5 mg apixaban twice a day.

Her symptoms had first improved on octreotide 0.5 mg (3/d). Unfortunately, only 12 days later, the patient was brought to the ICU due to massive diarrhoea (more than 10 stools/d), hypovolaemia (with consecutive pre-renal kidney failure) and hypokalaemia (lowest measured value was 2.4 mmol/l; normal range 3.5–4.8 mmol/l) and a rapidly deteriorating general condition: Pre-renal kidney failure progressed rapidly with normal values for creatinin (0.69 mg/dl; range 0.5–0.9 mg/dl) on 1 May, than 1.13 mg/dl on 2 May and 3.07 on 3 May with a glomerular filtration rate 20.5 ml/min (normal range > 60 ml/min). Metabolic acidosis with pH at 7.17, HCO3- 11.6 mmol/l and base excess (BE) of 16.8 mmol/l was measured. Values for sodium and chloride were in normal range. After electrolyte stabilisation and intensive volume substitution, we discussed all possible therapy options in an interdisciplinary setting. Since octreotide therapy and chemotherapy seemed not to be efficient in this patient's case and the symptoms were hardly manageable with symptomatic therapy, we favoured a surgical approach. However, we had to deal with metastatic VIPoma affecting both liver sites, so a curative intended surgery seemed unrealistic. Nevertheless, we decided to perform extensive surgery for symptom control with the goal of resecting >90% of the total tumour mass. We discussed all options with the patient, who also favoured the surgical approach, and obtained patient's consent to treatment. For the surgical procedure, we planned to remove the primary tumour by performing a distal pancreatectomy, and addressing the liver metastasis by performing a right hemihepatectomy (since the right lobe was almost completely interspersed by metastases, without an option to preserve functional liver parenchyma in the right lobe). For the left lobe, the atypical resection of superficial metastases was planned with the option to perform radiofrequency ablations (RFAs) for deeper metastases.

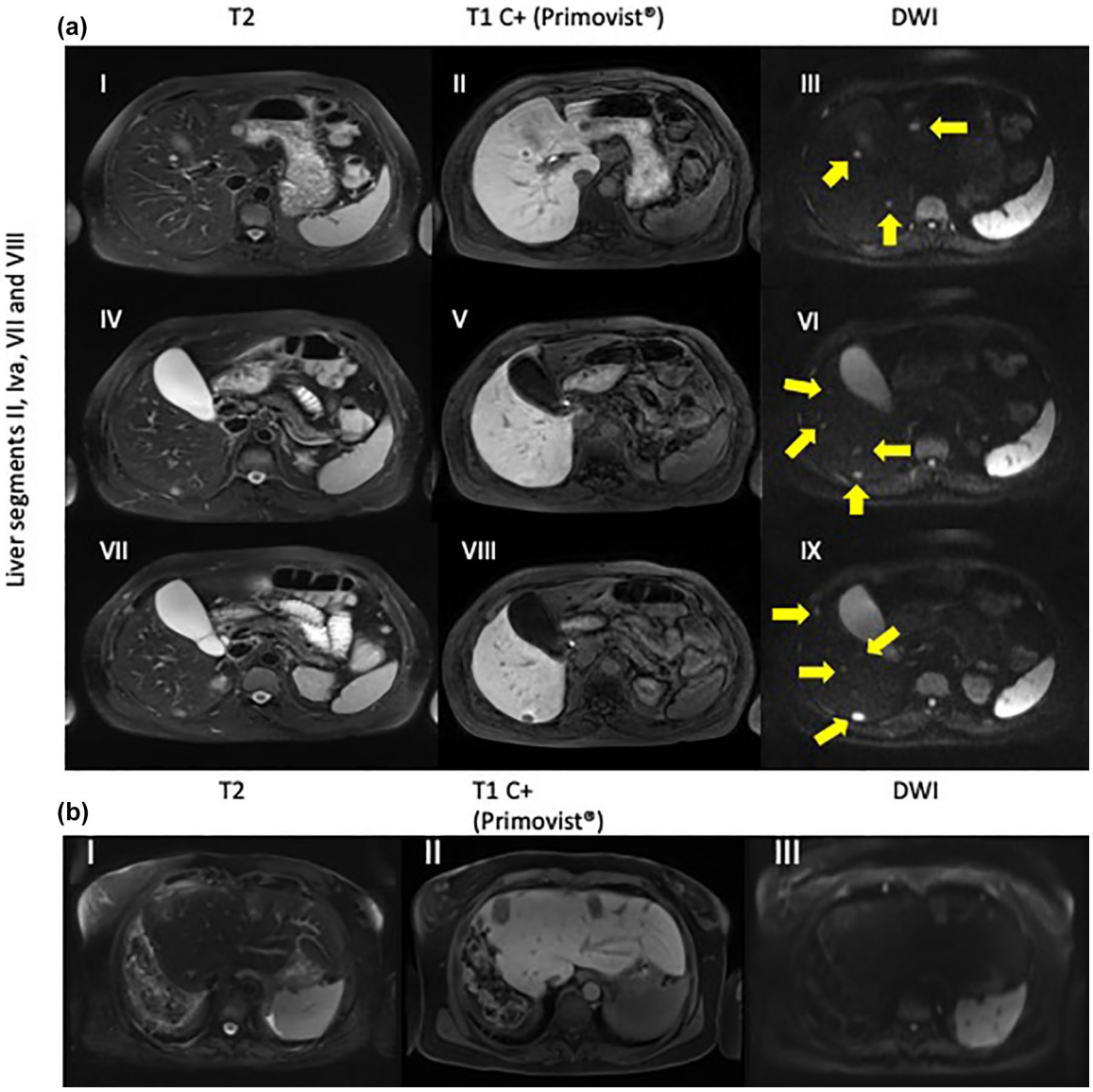

Figure 1. (a) Initial MRI scans of the liver (T2, T1C+ and DWI) before surgery showing the extent of liver metastasis of the VIPoma. Multiple lesions can be seen in liver segments II, IVa, VII and VIII (yellow arrows). Lesions are best detectable in DWI sequences. (b) Postoperative MRI scans during surveillance for 6 months. The images show resection defects and remnants after RFA without any indication of tumour recurrence.

After stabilising the patient, we performed spleen-preserving distal pancreatectomy, right hemihepatectomy, seven atypical liver resections and seven RFAs in liver segments II, III and IVa. In total, the surgery took 381 minutes and was performed without any intraoperative complications.

Postoperatively, the patient was brought to the ICU, where her recovery was uneventful. Somatostatin perfusion was reduced and finally stopped completely, early postoperative enteral nutrition was feasible, and the intraoperatively inserted drainages could be removed quickly. No events of diarrhoea or hypokalaemia occurred after the surgery.

A histopathological work-up showed a 1-cm tumour in the pancreatic tail with several hepatic metastases (up to 15 mm in diameter). The tumour was positive for synaptophysin and chromogranin. The proliferation rate (Ki67 index) was 6%. The TNM state was pT1 pN1 (1/3) L1

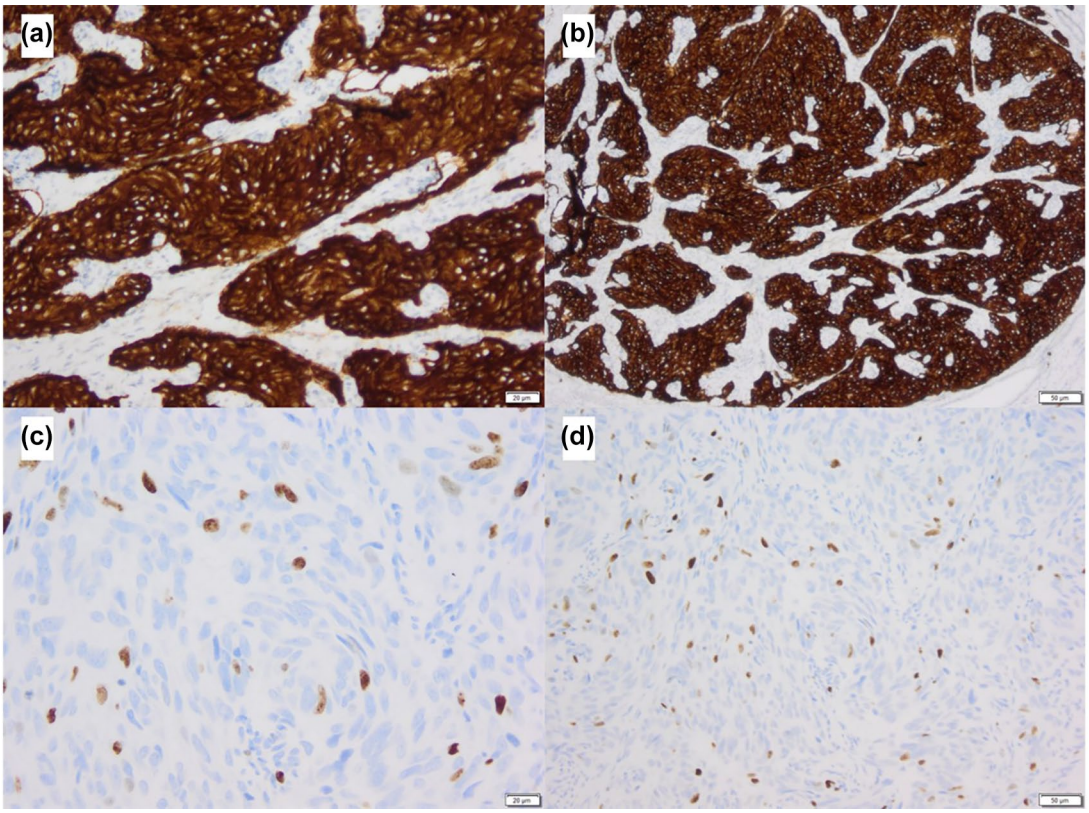

Figure 2. Representative images of immunohistochemical staining of the tumour resected from the pancreatic tail (immunoperoxidase on paraffin sections). Strong expression of (a) chromogranin and (b) synaptophysin. The Ki67 labelling index was 6% ((c) original magnification ×400; (d) original magnification ×200).

V1 M1 (hep) G2 R0. Interestingly, the resected tumour showed no signs of regression in the histopathological work-up (Figure 2). Therefore, we discussed the possible relevance of a postoperative chemotherapy in an interdisciplinary setting and decided against it, offering the patient a therapy-free time-period.

The patient was released from the hospital 22 days after surgery.

Two months after surgery, we performed the first follow-up. MRI showed no signs of remaining tumour mass, and the patient was in good health. No events of diarrhoea were reported. The second follow-up was 6 months after surgery. The patient was still in good health, and MRI showed no change (Figure 1(b)).

One year after the surgery, the patient was still in remission, in good health, and had gained weight. Eighteen months after surgery, CT scans showed recurrence of the disease. Multiple small liver lesions were detected while the patient was still asymptomatic and in good health without any ongoing treatment.

We discussed with the patient her site of view. Retrospectively, she felt that the past year without any treatment gave her the opportunity to catch up with her life. She was able to handle some issues of her two kids, help them staying in school or finishing school, respectively. They even went together for vacations for some weeks.

Literature review and discussion

In about 60–80% of all described VIPoma case patients presented with metastases of the VIPoma at primary diagnosis.[6,7] Leading symptom is diet-resistant diarrhoea, which can be as severe that the consequences (hypokalaemia, vasodilatation, anorexia, cramps) might be life-threatening. Treatment options include symptomatic therapy, chemotherapy, radiation and surgery. Currently many clinicians are reluctant towards surgical

approaches in metastatic VIPoma although patients have serious, even life-threatening symptoms and despite all efforts the effect of conservative methods is often limited. Besides somatostatin-analogues, possible chemotherapy options include sunitinib, everolimus, cetuximab, and rituximab.[8,9] Recently, treatment with lanreotide, temzolomide, and capecitabine are reported.[10] The effect of all of those mentioned is based on case reports and case series due to lack of prospective studies. Surgical approaches are considered as a possible option for metastatic VIPoma but not as standard procedure.[11] However, there are some publications about resected metastatic VIPoma reporting promising results.[12,13] In the present case, all conservative methods failed to relieve the patient from her severe symptoms. Due to resection of the primary tumour and its metastasis this young patient was for 1.5 years in remission. Even after 18 months, when the recurrence of VIPoma showed in scans, the patient was still asymptomatic and without any ongoing treatment or medication.

Conclusion

Surgical treatment of VIPoma is not only indicated in resectable non-metastatic VIPoma but it might also offer the best symptom control in case of diffuse hepatic metastasis of VIPoma.

Author contributions

AA and MG compiled all relevant information concerning that case and did the literature research, AK evaluated the whole treatment of the patient and contributed the relevant information concerning the conservative treatment of VIPoma, ASAH did the radiological analysis, JK covered the histopathological analysis, and AH and FS collected all relevant information from the time before the patient came to the University Medical Center Goettingen.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Informed consent

We obtained a signed consent of the patient for publishing the data and de-identified the data as far as possible. An ethics approval was not necessary for this case report.

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Supplemental material

Supplemental material for this article is available online.

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