CASE REPORT

Adrenal crisis in metastatic breast cancer

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SUMMARY

A female patient with oestrogen receptor-positive and human epidermal growth factor receptor 2 (HER2)-positive invasive lobular breast cancer presented with progressive disease on CT scan. Some days after initiation of antineoplastic chemotherapy and anti-HER2 targeted antibody therapy, the patient presented with profuse diarrhoea, neutropaenia, nausea and weakness. Although *Clostridium difficile* was rapidly tackled as a causative agent of gastrointestinal complaints, clinical situation did not markedly improve despite proper antimicrobial treatment. The patient reported profound lack of energy, while nausea, vomiting and loose stools still persisted. Additionally slightly exaggerated pigmentation of nonsunexposed skin and mucosal areas led us to the assumption of proopiomelanocortin-derived peptide hypersecretion. The combination of highly elevated adrenocorticotrophic hormone and low basal cortisol levels taken from a morning blood sample established the diagnosis of adrenal insufficiency due to metastatic burden, leading to a near Addison crisis by gastrointestinal complications of chemo-immune therapy. Administration of hydrocortisone immediately relieved general symptoms.

BACKGROUND

Adrenal insufficiency, first described by Thomas Addison in 1855,¹ is characterised by sometimes misinterpreted clinical cardinal symptoms like weakness, fatigue, anorexia, weight loss, hypotension, electrolyte disturbances and hyperpigmentation. Clinical picture is mainly generated by a deficient production of corticosteroids in relation to organism's demand and attributed to an impaired hypothalamic–pituitary–adrenal axis.

Specifically a precursor polypeptide called proopiomelanocortin (POMC) is released from the pituitary gland due to a feedback loop in response to lowered serum cortisol levels. Cleavage of the precursor molecule POMC leads to the enhanced production of adrenocorticotrophic hormone (ACTH) and to the accumulation of melanocyte-stimulating hormone, which results in exaggerated melanin production in skin melanocytes.²

Autoimmune adrenalitis in the Western world and infectious diseases, for example, tuberculosis targeting the adrenal glands, in less developed countries comprise the major causes of adrenal insufficiency.³

Although adrenal glands are a common site of metastatic involvement in many advanced malignancies, especially in lung cancer and also in some

specific breast cancer subtypes,⁴ severe adrenal impairments due to metastatic burden have only been described in single case reports.^{5–7}

Here we report on a case of a patient with advanced metastatic breast cancer including bilateral adrenal involvement, whose adrenal function subacutely deteriorated in response to a severe gastrointestinal adverse effect of chemoimmune therapy.

CASE PRESENTATION

A 47-year-old woman, in surveillance after intentional curative treatment of an oestrogen receptor-positive and HER2-positive invasive lobular breast cancer first diagnosed in 2001, experienced progressive disease displaying new malignant lesions in the liver, lung, retroperitoneal lymph nodes and adrenal glands on CT scan (figure 1; arrowheads). The remaining medical history apart from breast cancer was unremarkable. Some days after administration of a combination of antineoplastic chemo-immune therapy according to the Cleopatra trial,⁸ the patient presented with profuse diarrhoea, nausea and bedriddenness.

Re-evaluation of the patient's recent complaints revealed a steadily declining general health condition over the last weeks as reported by her family members — symptoms that we attributed to tumour fatigue due to progressive disease during her last admission.

Physical examination on admission revealed an elevated body temperature of 39°C in a dehydrated patient with hypotensive blood pressure and unable to stand up without collapsing.

Laboratory measurements indicated neutropaenia grade II; in addition, mild hyponatraemia of 128 mmol/L with high normal potassium values of 4 mmol/L was present. The ECG showed deep inverted T waves on the precordial leads with prolonged QT time of over 500 ms in the absence of ischaemic physical symptoms and no elevated cardiac enzymes in repetitive blood samples (figure 2).

We initiated Ringer lactate infusions combined with broad spectrum antibiotics supported by granulocyte colony stimulating factor (G-CSF). Blood and stool cultures were taken, and *Clostridium difficile* could be identified as a causative diarrhoeal agent and antibiotic treatment was adapted appropriately.

Despite proper therapy clinical situation did not markedly improve over the next days. The patient felt significantly distressed and reported profound lack of energy, while nausea, vomiting and loose stools persisted. Other causes of chemotherapy-associated

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Figure 1 Abdominal CT scan showing liver metastases and prominent nodular, enlarged adrenal glands (arrowheads), highly suspicious of metastatic involvement.

diarrhoea were considered, such as docetaxel-associated colitis,⁹ neutropaenic colitis¹⁰ or cytomegalovirus colitis,¹¹ but clinical picture did not really fit into one of these categories.

On clinical follow-up we observed a slight but increasing brownish pigmentation of the face (figure 3) and — at a closer look — also of non-sun-exposed skin areas like lips or tongue (figure 4), and grooves of the palmar hand were affected (figure 5). The assumption of POMC-derived peptide hypersecretion was feasible, which guided the diagnosis of adrenal insufficiency. We immediately provided intravenous hydrocortisone irrespective of the results of adrenal testing. The patient's clinical condition improved dramatically within some hours.

The combination of highly elevated ACTH and low basal cortisol levels taken from the following blood sample on the following day finally established the diagnosis of adrenal insufficiency.

Figure 2 ECG with pseudoischaemic pattern and prolonged QT time.

Figure 3 Bronze-brown tanned face in response to elevated proopiomelanocortin levels.

Re-evaluation of the abdominal CT scan was performed some weeks before confirmed bilateral adrenal infiltration, whose clinical consequences might have been underestimated before given the fact that probable complications of chemotherapy might give rise to exhaustion of adrenal reserve and evolvement of adrenal crisis.

To substitute adrenal function we established a regular hydrocortisone dose twice daily (morning and afternoon), and on clinical follow-up the patient was dramatically improving, returning back to working life. Further chemotherapy cycles could be applied without any interruption. An instruction for emergency situations and consecutive self-dependent increment of hydrocortisone dosing was provided to the patient.

DISCUSSION

Metastases to the adrenal glands are frequently reported in patients with breast cancer. Pattern of metastases seems to be

Figure 4 Dark spots on tongue and lips caused by Addison disease.

Figure 5 Prominent discolouration of palmar creases as reported in adrenal insufficiency.

dependent on the histological subtype, providing a slight predilection for lobular breast cancer according to recent investigations.^{12–14} Especially patients younger than 50 years of age have a higher propensity for adrenal metastases. Importantly adrenal metastases appear to have a crucial role for prognosis as there is a strong correlation between extensive glandular involvement and overall survival.¹²

Nevertheless adrenal insufficiency due to metastatic disease in breast cancer is a rather rare incident. Descriptions are commonly based on isolated case reports as it requires a more than 90% destruction of the adrenal parenchyma to cause clinically overt adrenal insufficiency.¹⁵

Destruction of parenchyma in metastatic disease might not solely be caused by replacement of adrenal glands by metastatic tissue, but may also include haemorrhagic necrosis of adrenals in the context of metastatic infiltration, and impaired adrenal synthesis in patients being treated with specific anticancer drugs or metastases to the pituitary gland causing secondary adrenal insufficiency.

In our case nodular enlargement of both adrenal glands suggested infiltrating metastatic tissue. We do not have any evidence to assume chemotherapy-associated impairment of corticosteroid synthesis, as there is no correlation with docetaxel, trastuzumab or pertuzumab described in the literature.

However, it has also been reported on the molecular level that elevated glucocorticoid levels may be tied to altered sensitivity of breast cancer cells to chemotherapeutics.¹⁶

In addition enhanced glucocorticoid signalling may even be associated with adverse prognosis in several solid tumours like prostate cancer.¹⁷

We speculate that withdrawal of steroids included in the anti-cancer protocol as a pretreatment in combination with *C. difficile* caused diarrhoea, a well-established risk factor of adrenal crisis,¹⁸ and led to acute deterioration of adrenal function in the background of impaired adrenal reserve. Our case might be in discrepancy to a former trial highlighting the role of large macrometastases in the development of adrenal insufficiency, as our CT scan only detected a moderate nodular enlargement.¹⁹

This might underpin the fact that if a patient with advanced cancer presents with unexplained and protracted fatigue and exhaustion combined with prominent gastrointestinal complaints, for example nausea, vomiting and diarrhoea, adrenal insufficiency should be part of differential diagnostic considerations, particularly if accompanied with electrolyte abnormalities and ECG changes.²⁰ Pseudoischaemic alterations of cardiac repolarisation are described as a prominent feature in adrenal crisis, and its aetiology still remains unclear,^{21 22} whereas ECG patterns due to corticosteroid deprivation induce electrolyte abnormalities, for example hyperkalaemia.

This case adds more evidence that patients with bilateral adrenal metastases should be carefully evaluated for the presence of adrenal insufficiency and should receive careful observation, even if baseline values are normal, as patients with cancer are especially prone to triggers for adrenal deterioration.²⁰ Differential diagnostic considerations should include progressive disease with increasing tumour fatigue, side effects of anticancer therapy, hyperkalaemia or new brain metastases.

Substitution of hydrocortisone mimicking adrenal function will substantially improve the quality of life of patients with cancer even in the palliative setting. Furthermore careful monitoring for triggers of adrenal crisis, as well as consecutive adaptation of dosing due to stressful events, will prevent acute deterioration and premature death.

Learning points

- Adrenal insufficiency should be considered in patients with cancer with metastatic disease presenting with unexplained nausea, vomiting, weakness and exaggerated fatigue, particularly if accompanied by electrolyte changes.
- Complications/side effects of chemotherapy, for example, gastroenteritis and fever, require prompt adaption of hydrocortisone substitution in order to avoid adrenal crisis.
- Patients with bilateral adrenal metastases should be evaluated for the presence of adrenal insufficiency and need careful follow-up.
- The treating clinician should be aware of pseudoischaemic ECG patterns in adrenal crisis in order to avoid unnecessary invasive cardiac procedures.

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