CASE REPORT

Adrenocortical carcinoma mimicking lung cancer and responding to vinorelbine/carboplatin and pemetrexed/carboplatin

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SUMMARY

Adrenocortical carcinoma is an aggressive cancer, with an incidence of 0.5–2 per million. We present a case of adrenocortical carcinoma with all the clinical and partly immunohistochemical features of disseminated undifferentiated lung cancer, and ‘accidentally’ treated as such. Four cycles of carboplatin–vinorelbine conferred partial response in the adrenal, lung and disappearance of a 2 cm subcutaneous iliac nodule that had appeared suddenly before the first course. Owing to progression, four cycles of carboplatin–pemetrexed were administered inducing partial response and then stable disease for an additional 12 months. As fluoro-D-glucose (FDG)-positron emission tomography (PET) only showed activity in the adrenal, laparoscopic adrenalectomy was performed. Three months later FDG-PET revealed a lung nodule unresponsive to carboplatin–pemetrexed, removed by wedge resection. Finally, re-evaluation by a tertiary centre confirmed adrenocortical carcinoma with Ki67—50% in the adrenal and the lung. The patient is alive and tumour free almost 3.5 years after retrospective diagnosis of metastatic adrenocortical cancer.

regrettably showing no statistical difference in overall survival.⁹

In clinical practice, sometimes there are unpleasant surprises, such as in this case, where the patient had been treated for what we believed was advanced lung cancer for 2.5 years until we realised he had a metastatic ACC. Mistakes are failures that clinical doctors would usually not want to publicise. However, given the rarity of ACC and how it mimicked metastatic lung cancer, it is clearly a case that we learned from and would naturally want to share with our colleagues. Moreover, the lung cancer chemotherapy regimens seemed to benefit our patient with minor side effects. There are no previously published accounts of these combinations for treating ACC. This ‘accidental’ treatment response is also a valid reason to share this case history, as the 1-year survival of metastatic ACC still is only 15%. Without knowing that it was ACC, the multidisciplinary team decided to perform relatively aggressive surgery based on fluoro-D-glucose (FDG)-positron emission tomography (PET) findings, which retrospectively was correct, as surgery is the only curative treatment of ACC.¹

BACKGROUND

Adrenocortical carcinoma (ACC) is a rare but aggressive cancer, with an incidence of 0.5–2 per million; it has a bimodal age distribution with a peak in children <5 years old and adults between 4th and 5th decade of life.^{1–3} Some cases are associated with rare genetic syndromes, such as the Beckwith-Wiedemann syndrome in childhood ACC, and in adult cases the Li-Fraumeni, multiple endocrine neoplasia type 1 (MEN1) and Lynch syndrome.^{4–5} The prognosis of this disease is dismal as the diagnosis usually presents at an advanced stage and the median survival is 12 months.⁶ Surgery may be curative but relapse is common even in early stages. Adjuvant treatment with mitotane, a peroral drug, has shown a survival benefit in a retrospective study of 177 patients. Mitotane was approved for this disease more than 40 years ago;^{7–8} it is a compound derived from the insecticide DDT. Its mode of action is inhibition of adrenocortical cells and their production of hormones. In the metastatic setting, several phase I–II trials with combinatorial regimens have failed, but a recent large randomised study showed that etoposide, doxorubicin and cisplatin plus mitotane were superior to streptozocin plus mitotane, increasing progression-free survival from 2.1 to 5 months, but

Ethical considerations

Informed consent was obtained from the patient prior to writing this manuscript.

CASE PRESENTATION

The patient, a woman in her early 50s, had rheumatoid arthritis for several years, which was treated with methotrexate; there was no family history of cancer. She had smoked for the past 30 years but quit the previous year. She had no weight loss or other symptoms of an advanced cancer and was WHO performance status 0. In May 2011, she was admitted to our hospital with acute pain of the right flank. An ultrasound scan showed intra-parenchymatous bleeding of the right adrenal gland. No definite aetiology was established. The lesion was increasingly painful and the patient had several hospital admissions because of this.

INVESTIGATIONS

Subsequent CT scan at our hospital showed a lung tumour in the right upper lobe, multiple suspect metastatic nodules in both lungs and a cystic tumour in the left adrenal gland. The CA19-9 was marginally elevated (27kIE/L, range 0–27) and the

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chromogranin A (CGA) fivefold (15.3 nmol/L, range 0–3), carcinoembryonic antigen (CEA) sevenfold (36 ng/mL, range 0–5) while CA125 and neuron-specific enolase (NSE) were normal (figure 1). The patient also had mild anaemia and leucocytosis.

A CT-guided Tru-cut lung biopsy from one of the metastases showed only atypical epithelial cells, positive CKAE1/AE3 and negative CK5/6, CK7, TTF1. An ultrasound-guided biopsy of the affected adrenal gland showed undifferentiated malignant

Figure 1 Time-line from the first diagnosis, positron emission tomography (PET)-CT findings, treatments, responses and biomarkers. CA19-9 is an epithelial tumour marker of the upper gastrointestinal tract and chromogranin A (CGA), CGA is a neuroendocrine marker. The CGA, even if very high, does not seem to follow the clinical pattern, while CA19-9 seems to follow the response after the pemetrexed-carboplatin treatment.

cells and immunohistochemistry showed positive CKAE1/AE3 and vimentin and negative CK5/6, CK7, TTF1, BerEp4, chromogranin, synaptophysin, S100 and smooth muscle actin (SMA). No mutation in EGFR (epidermal growth factor receptor) gene exon 18–21 was found. For the evaluation of the extent of malignancy, an 2-deoxy-2-[^{18}F]FDG PET/CT was performed in July 2011. The ^{18}F -FDG PET/CT revealed increased ^{18}F -FDG uptake in a spiculated tumour in the right upper lobe, which had grown from 6 to 18 mm in 3 years, and several small new lesions in the right and left lower lobe (figure 2; ^{18}F -FDG PET/CT).

DIFFERENTIAL DIAGNOSIS

The primary pathologist's report stated that the diagnosis could be ACC, but that cytokeratin CKAE1/AE3 positivity was not consistent with that, and thus primary lung cancer could not be ruled out. Moreover, negative TTF1 do not exclude the lung cancer diagnosis. Chromogranin and synaptophysin in the tumour were negative, excluding a neuroendocrine tumour, which made the elevated serum CGA unexplainable. As the histology did not give a clear answer on the origin of the tumour, the clinical and radiological picture aided diagnosis. The patient had smoked cigarettes for many years, ^{18}F -FDG PET/CT picture was consistent with primary lung tumour with metastasis to the lung and right adrenal, and the oncologist (ODR) and the pulmonary specialist (PAO) both agreed that the diagnosis of undifferentiated metastatic non-small cell lung cancer (NSCLC) was the most plausible.

TREATMENT

The patient received our standard treatment for metastatic NSCLC, four courses of carboplatin (AUC5, days 1 and 22) and

vinorelbine (55 mg days 1, 8 and 22), which were well tolerated with only minor fatigue and without delays. A subcutaneous nodule 2 cm in diameter in the left iliac, which had rapidly developed before start of treatment, disappeared after two courses, indicating chemosensitive disease. Evaluation by CT in October 2011 showed partial remission of all manifestations. A CT in December 2011 showed an increase in size of the 'primary' lung tumour but regression of the other lung lesions. Another CT scan performed in January 2012 showed new small lesions in both lungs. Now the CEA was normalised, CA19-9 had almost doubled and CGA was elevated 33-fold. CA19-9 can be elevated in lung carcinomas, and we speculated whether the massively elevated CGA was due to a tumour clone that was not apparent in the biopsies (figure 1).

Owing to the rapid recurrence of new lesions and an apparent non-squamous NSCLC diagnosis, four courses of pemetrexed (800 mg days 1 and 22) and carboplatin (AUC5 days 1 and 22) were administered from February to April 2012. There was a complete response of the lung tumour and some of the metastatic nodules in the lungs as well as a marked shrinkage of the adrenal tumour. These courses were also well tolerated with minor side effects.

In November 2012, methotrexate and steroids were reinstated due to increasing rheumatoid arthritis symptoms.

CA19-9, an epithelial tumour marker of the upper gastrointestinal tract and CGA, a neuroendocrine marker, were repeatedly measured due to elevated values. The CGA, even if very high, did not appear to follow the clinical pattern, while CA19-9 appeared to follow the response after the pemetrexed-carboplatin treatment (Time-line from the first diagnosis, PET-CT findings, treatments, responses and biomarkers are summarised in figure 1).

Figure 2 Fluoro-d-glucose (^{18}F -FDG)-positron emission tomography (PET) images: (A and C) Coronal PET/CT images. (B and D) Axial PET/CT images of upper abdomen pre-treatment 2011 (lower row) revealed increased uptake of ^{18}F -FDG in a solid component of the right adrenal tumour, which changed in size and uptake after treatment and 1 year with no treatment. The tumour got smaller, but the intensity was increased (upper row).

Figure 3 Fluoro-D-glucose (^{18}F -FDG)-positron emission tomography (PET) images: (A and C) Maximum intensity PET projection images showed increased uptake in the solid component of a right adrenal tumour at both time points. Increased ^{18}F -FDG uptake in five lung lesions suggestive of malignancies detected at the pre-treatment PET/CT examination from July 2011 (C) and increased uptake due to a fracture in the right 4th costa (A). (B and D) Axial PET/CT images of the thorax revealed increased uptake in a lung lesion in lobus inferior in July 2011 (D). No ^{18}F -FDG uptake in two remaining lung lesions were seen at the PET/CT examination before adrenalectomy from March 2013 (C). Unchanged uptake in a fracture of the right 4th costa (C).

Figure 4 Fluoro-D-glucose (^{18}F -FDG)-positron emission tomography (PET) images 5 months after adrenalectomy showing increased uptake only in one node of the right upper lobe (arrows), which subsequently was radically removed.

Figure 5 Immunohistochemistry: (A) Needle biopsy from adrenal. (B) Lung surgical sample with pleomorphism and necrosis. (C) Immunostaining with Ki67 and Melan A. (D) Vimentin immunostaining. (E) Keratin immunostaining. (F) Calretinin immunostaining.

OUTCOME AND FOLLOW-UP

Surprisingly, the situation stabilised without any treatment with a progression free interval of 1 year, and an ^{18}F -FDG PET-CT in March 2013 showed stable but active disease only in the right adrenal gland (figures 2 and 3). The tertiary centre MDT meeting decided to operate and the adrenal gland was laparoscopically extirpated in May 2013.

A control CT 2 months later revealed a 3 mm nodule in the right upper lobe and 1 month later the size was increased to 8 mm. After re-induction with three courses of pemetrexed–carboplatin, this solitary nodule progressed to 19 mm in October 2013. A full-body ^{18}F -FDG PET/CT in October 2013 showed uptake only in this nodule (figure 4). Wedge excision of the tumour was performed in November 2012 by video-assisted thoracoscopy and the histology was identical with that of the adrenal, undifferentiated carcinoma.

Owing to uncertainty of the diagnosis, our pathologist required re-evaluation of the PET-positive lung tumour and adrenal gland at the tertiary centre at Oslo University Hospital (OUS). Gross inspection of the lung and adrenal specimens displayed delineated heterogeneous, white-yellow viable to red necrotic tumours with apparent clear margins. Microscopically, a diffuse growth pattern interrupted by necrotic areas was found.

Irregular epithelioid cells with eosinophilic cytoplasm were predominant, but giant cells with nuclear pleomorphism and hyperchromasia were also seen throughout the tumour with groups of atypical spindle cells. No specific mesenchymal or oncocyctic differentiation was identified. The average mitotic activity was 15/10 high-power fields (HPFs), the proliferation index Ki67 was 50% and multiple atypical mitotic figures were seen. An immunohistochemical panel showed that the tumours were diffusely positive for vimentin, patchy positive for AE1/AE3 keratin and Melan A, and multifocal clusters of tumour cells stained for calretinin. Negative staining was seen for EMA, CK7, CK20, CK5/6, BerEP4, TTF1, chromogranin, synaptophysin, S-100, SMA, inhibin and CD117c-kit (figure 5). Based on tumour morphology and immunoprofile the final diagnosis was pleomorphic ACC. The patient was then started on adjuvant mitotane, is still alive and tumour free 3 years and 4 months after the retrospective diagnosis of metastatic adrenocortical cancer.

DISCUSSION

Metastatic NSCLC has a median survival of 12 months and metastatic ACC has a 1-year survival of only 15% with even fewer treatment options.⁹ This disease is generally considered to be chemoresistant, however, there are case reports of long-term

survivors of advanced ACC treated in a multimodal fashion.¹⁰ In a large recent trial on ACC, combinations of mitotane with etoposide, doxorubicin and cisplatin were tried, without improving overall survival.⁹ In a small retrospective series radiotherapy was seemingly effective in a palliative setting with clinical or radiological responses in 10 of 12 cases.¹¹ The current case is presented because it has important teaching points regarding diagnosis and treatment of this rare cancer.

The first lesson is the difficulty of obtaining a correct clinical and pathological diagnosis of ACC, especially when the clinical presentation apparently does not fit with the suggested diagnosis. In this case our patient was primarily treated under the diagnosis of a disseminated NSCLC, with metastasis to the right adrenal; it was only later that it was revealed to be quite the opposite, an ACC with metastasis to the lungs. An important clinical detail was the presentation of the cancer with bleeding in the adrenal tumour. In a large series of adrenal bleeding, 6.4% had adrenal neoplasm and 10/14 cases were metastatic. However, as an ACC is rare, there is a much higher possibility that adrenal bleeding could represent a primary ACC.¹² The re-evaluation in a tertiary centre concluded that the morphologic features were strongly suggestive of a pleomorphic ACC. Diagnosis of an ACC is not easy, as it shares several similarities with other types of cancers.¹³ The ACC has no pathognomonic immunohistochemical profile,¹⁴ but positive immunostaining for vimentin, Melan A and calretinin, and negative CK7, BerEPA4 and TTF1 staining strongly support the diagnosis. The tumours in this case additionally stained positive for cytokeratin AE1/AE3. Although AACs are typically cytokeratin negative, some studies have reported ACCs with cytokeratin positive cells,^{15–17} and a recent publication refers to approximately 20% positive staining for CAM5.2.³

The second lesson was the surprising effect of vinorelbine, an antitubuline and pemetrexed multifolate inhibitor in combination with carboplatin, when we realised that the patient had ACC. Both these regimens were clearly active in all manifestations, in the lungs as well as in the adrenal tumour, and it seems that there were two populations of the tumour, the first vinorelbine sensitive and the second pemetrexed sensitive. The largest reduction of tumour was seen with the first-line treatment with vinorelbine–carboplatin, but shortly after four cycles some small lung lesions emerged that were not seen previously. These were reduced after four cycles of pemetrexed–carboplatin. This indicates a separate effect of the two drugs combined with the carboplatin. Monotherapy of carboplatin has not been published, but there are reports of the effect of cisplatin monotherapy. The progression free interval without treatment for over 1 year after second-line treatment was also not expected, nor was the disappearance of ¹⁸F-FDG-positive lesions in the lung, while the tumour in the adrenal gland still maintained metabolic activity (figures 2 and 3). To the best of our knowledge there are no published reports on ACC treated with pemetrexed or vinorelbine. In this case we verified partial response with compounds and relapse-free survival of over 2 years. Is there any molecular rationale that these compounds should be effective in ACC? Several molecular features of ACC could explain the effect of these compounds as overexpression of the TOP2A.¹⁸

Finally, the wrong diagnosis could have lead to treatment inferior to that which is recommended, and to toxicities due to non-recommended treatment and even worse outcome. The adrenal and the lung lesions were not eradicated by the chemotherapy. However, successful radical surgery of remaining PET-positive lesions and no local relapse in either site after excision seem to have prolonged this patient's life.

Learning points

- Adrenocortical carcinoma diagnosis can be missed due to clinical and morphological similarities with other cancers. Owing to the rarity of this cancer, a well-founded suspicion should elicit an early second opinion at a referral centre.
- In this case, new chemotherapy doublets, vinorelbine–carboplatin and pemetrexed–carboplatin showed clinically meaningful effect in this case of metastatic adrenocortical carcinoma.
- Radical surgery of remaining positron emission tomography-positive lesions seems to have prolonged this patient's life.

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Contributors ODR treated the patient and wrote the manuscript. PAO also followed and treated the patient and contributed to the manuscript. M-ER performed the PET-CT analysis and co-wrote the manuscript. AS performed the immunohistochemistry and co-wrote the manuscript.

Competing interests None.

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