Addison's disease due to metastases to the adrenal glands

F. Mor1, M. Lahav1, E. Kipper2 and A.J. Wysenbeek1

1Department of Internal Medicine B and 2Radiology Department, Beilinson Medical Center, Petah Tiqva and The Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

Summary: A 43 year old patient with Addison's disease secondary to extensive metastases to both adrenal glands is presented. Thirty two previously reported cases are reviewed; in only 13 cases was the diagnosis of Addison's disease confirmed biochemically. Reasons for the apparent rarity of Addison's disease in spite of the frequency of adrenal metastases are discussed. The need to consider the possibility of Addison's disease complicating known malignant disease arising in other tissues is stressed.

Introduction

The adrenal glands are the fourth most common site of distant metastases after lung, liver and bone (Willis, 1953). The incidence of metastatic involvement of the adrenals is especially high in bronchogenic and breast carcinomas (Glomset, 1938). On the other hand, clinical adrenal insufficiency secondary to metastases is very rare. In reviewing the literature we have found only 13 proven cases (Alpers et al., 1962; Butterly et al., 1952; Galloway & Perloff, 1960; Heath & Bergeuin, 1973; Herison, 1966; Rosenthal et al., 1978; Sahagian-Edwards & Holland, 1954; Vieweg et al., 1973; Zimm et al., 1981). In all these patients the diagnosis was made by endocrinological tests, and in all of them except one (Zimm et al., 1981) the presence of bilateral adrenal metastases was confirmed at autopsy.

Here we present a case of Addison's disease secondary to metastatic involvement of both adrenal glands, diagnosed by laboratory methods and computed tomography (CT) scan, and confirmed at autopsy. A review of the relevant literature is presented.

Case report

A 45 year old man was admitted because of generalized weakness, fever, anorexia, nausea and vomiting.

Seven years previously the patient had undergone anterior resection of the colon for adenocarcinoma, followed by postoperative pelvic irradiation and treatment with 5-fluorouracil. Six years later the patient complained of cough and weight loss and X-ray of the chest revealed a density in the right middle lobe with right pleural effusion. Bronchoscopy showed an endobronchial lesion which on biopsy was shown to be adenocarcinoma. A thoracotomy was performed in which a mass was found in the right middle lobe extending to the hilum and a liver mass was palpated through the diaphragm. The lung mass was not excised and biopsies confirmed the diagnosis of adenocarcinoma. Post-operatively the patient received another course of 5-fluorouracil.

On admission, 1 y after the thoracotomy, his temperature was 37.8°C, the heart rate was 80 beats/min, and the blood pressure 80/60 mm Hg. Diffuse hyperpigmentation of the skin was noted. Chest X-ray showed multiple metastases in the left lung. Cultures of blood, urine and throat were negative. Serum sodium and potassium were 130 mmol/l and 6.3 mmol/l, respectively. Serum ACTH level was 520 pg/ml (normal < 80 pg/ml). The basal concentrations of serum and urinary steroids were obtained and a Synacthen test was performed (Table I).

In view of the recent complaints, the physical examination and the data shown in Table I, the

<table>
<thead>
<tr>
<th>Table I</th>
<th>Urinary and serum corticosteroids before and after Synacthen stimulation test</th>
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<tbody>
<tr>
<td></td>
<td>Basal</td>
</tr>
<tr>
<td>Urinary 17-ketosteroids mg/24 h</td>
<td>5.6 (7–25)</td>
</tr>
<tr>
<td>Urinary 17-hydroxycorticoids mg/24 h</td>
<td>11.9 (2–10)</td>
</tr>
<tr>
<td>Urinary 11-hydroxycorticoids µg/24 h</td>
<td>75.0 (50–150)</td>
</tr>
<tr>
<td>Serum cortisol µg/dl</td>
<td>14.8 (5–20)</td>
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Correspondence: F. Mor, M.D., Department of Internal Medicine B, Beilinson Medical Center, 49 100 Petah Tiqva, Israel

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diagnosis of Addison's disease was made. A CT scan of the abdomen disclosed multiple metastases in the liver, a 7 cm mass in the area of the right adrenal displacing the vena cava anteriorly, and a 9 cm mass in the area of the left adrenal displacing the splenic vein and the tail of the pancreas anteriorly (Figure 1). An intermediate strength PPD skin test was negative, and no adrenal antibodies were demonstrated.

Treatment was started with prednisone, 15 mg/d, followed by rapid symptomatic improvement. Four months later the ACTH level was 48 pg/ml.

Eight months later the patient was readmitted complaining of severe dyspnoea. Chest X-ray showed multiple metastases in both lung fields. The patient died a few days later in respiratory failure. Localized post mortem examination of left flank was performed in which a 5 x 10 x 16 cm spherical mass was found in the left adrenal. Microscopic examination revealed adenocarcinoma with areas of necrosis. No adrenal tissue could be found.

Discussion

In the patient described, Addison's disease was diagnosed on the basis of the clinical picture and laboratory evaluation. The most probable cause of the adrenal insufficiency was extensive bilateral metastases, visualized on CT scan and later verified at autopsy.

In reviewing the literature we found 32 cases of Addison's disease claimed to be caused by metastases to the adrenals (Addison, 1855; Alpers et al., 1962; Bullock & Hirst, 1953; Butterly et al., 1952; Galloway & Perloff, 1960; Guttman, 1930; Heath & Bergehal, 1973; Herison, 1966; Hill & Wheeler, 1965; Rosenthal et al., 1978; Sahagian-Edwards & Holland, 1954; Vieweg et al., 1973; Zimm et al., 1981) (Table II). The diagnosis of adrenal insufficiency was confirmed by measurements of steroid levels and ACTH stimulation tests in only 13 patients.

Addison's disease has also been reported in two patients suffering from Hodgkin's disease (Feinmann, et al., 1976) and malignant lymphoma (Osei et al., 1983). These patients presented with Addison's disease and the adrenals were found to be infiltrated by the lymphoproliferative process.

Since the symptoms of extensive metastatic disease can be very similar to those of Addison's disease, one can accept as proven cases only those confirmed by endocrinological investigations.

The frequency of metastases to the adrenal glands in autopsy series of cancer patients ranges from 8.6 to 27% (Abrams et al., 1950; Glomset, 1938; Guttman, 1930; Willis, 1953). As many as 58% of patients with breast carcinoma, 36% with lung cancer and 33% of patients with melanoma have been found at autopsy to have adrenal metastases (Glomset, 1938, cited from Zimm et al., 1981). Thus it is surprising that Addison's disease has only rarely been reported in cancer patients.

In a group of 566 cases of Addison's disease, metastatic carcinoma was the aetiological factor in 1% (Guttman, 1930). The following points must be kept in mind in order to understand the extremely low incidence of reported Addison's disease caused by metastases. In spite of the frequent involvement of the adrenal glands by the malignant process: (1) more than 80% of the total adrenal cortical tissue may be replaced by tumour without evidence of adrenal hypofunction (Cedermark & Sjoberg, 1981); (2) the symptoms of metastatic disease in its terminal stages coincide with many of the clinical symptoms of adrenal insufficiency (Hill & Wheeler 1965); (3) many treatment protocols include steroids that may mask the presence of Addison's disease. In some of these patients, even when the diagnosis of Addison's disease is made, it might have been attributed to withdrawal of steroids. Bearing these points in mind, Addison's

<table>
<thead>
<tr>
<th>Primary site</th>
<th>No. of cases</th>
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<tbody>
<tr>
<td>Lung</td>
<td>19</td>
</tr>
<tr>
<td>Breast</td>
<td>3</td>
</tr>
<tr>
<td>Stomach</td>
<td>3</td>
</tr>
<tr>
<td>Uterus</td>
<td>1</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1</td>
</tr>
<tr>
<td>Adrenal carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Seminoma of testis</td>
<td>1</td>
</tr>
<tr>
<td>Unknown primary</td>
<td>3</td>
</tr>
</tbody>
</table>
disease secondary to metastases to the adrenals is probably more prevalent than appears from the literature.

The clinical setting in which Addison’s disease develops in cancer patients is usually at a time when the malignant disease is in an advanced stage. However, in 4 patients (Herison, 1966; Rosenthal et al., 1978; Sahagian-Edwards & Holland 1954), Addison’s disease was the presenting syndrome of the malignant process.

Since the response to replacement therapy is usually dramatic and results in significant palliation, it is important to consider Addison’s disease in the cancer patient who has progressive anorexia, malaise and weight loss, especially if accompanied by hypotension, hyperpigmentation or electrolyte imbalance. Although the disease will be diagnosed infrequently, it is imperative to bear this diagnosis in mind and to perform the appropriate tests.

References


GUTTMAN, P.H. (1930). Addison’s disease, a statistical analysis of 566 cases and a study of the pathology. Archives of Pathology, 10, 742.


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