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REVIEW

Adrenal metastases

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Abstract: The adrenal gland is a frequent location for metastatic spread of a various number of malignant tumors. Among all tumors, carcinoma of lung, breast, ovary and malignant melanoma count to the most frequent ones. In nononcological and unselected populations, the prevalence of adrenal metastases is 0–21 %. The metastases are mostly discovered in patients during their follow-up carried out in consequence of their antecedent malignant disease. A malignant disease in adrenal gland may occasionally manifest as a solitary metastasis referred to as adrenal incidentaloma. If the malignant disease is disseminated at the time of adrenal mass diagnosis, no further differentiation of lesion is necessary as it does not influence the further therapeutic process. If the dissemination is not present, further differentiation of adrenal lesion is essential. CT and MRI characteristics of the adrenal mass play the key role in the differential diagnosis. The examination of adrenal overproduction is not necessary in case of known adrenal metastasis except when performing tests in order to rule out the catecholamine overproduction. In case of bilateral metastases, adrenal insufficiency should be also excluded. Surgical treatment is indicated in cases of solitary metastasis. The further management of patients with adrenal metastases belongs to the oncologist. The prognosis of the disease is usually very poor with average survival rate of three months *(Fig. 2, Ref. 34)*. Full Text in PDF *www.elis.sk.*
Key words: adrenal metastases, imaging of adrenal tumors, adrenal incidentalomas, pheochromocytoma.

The adrenal gland is a frequent location for metastatic spread of a various number of malignant tumors. Theoretically, every primary malignancy may disseminate into adrenal glands. Among all tumors, carcinoma of lung, breast, ovary and malignant melanoma count to the most frequent ones. Stomach cancer represents a less common cause of adrenal metastases while the potential of oncocytoma to spread into adrenal glands has been described as rare (1). Malignant lymphoma is being described as relatively frequent cause of bilateral adrenal infiltration.

Epidemiology

In nononcological and unselected populations, the prevalence of adrenal metastases is 0–21 %. In oncological patients, the prevalence is referred to be higher, namely in range of 32–73 % (2). Lenert et al report similar rates based on their finding that 52 % of adrenal masses in 91patients with a recently diagnosed extra-adrenal malignancy were metastatic (3). Meta-analysis of Cawood et al has shown that the estimated real prevalence is approximately 2.3 % while higher occurrence is usually overestimated and originates from differently selected groups (4).

Autopsy studies in patients with malignant tumors of epithelial character have documented the prevalence of metastases to be even 27 % (5, 6). The occurrence rates of adrenal metastases in patients with breast carcinoma and lung carcinoma are 39 % and 35 %, respectively (5, 6, 7). Adrenal involvement is found in 46.8–50 % of cases with malignant melanoma (8, 9). The adrenal gland is the second most common site of metastases from hepatocellular carcinoma (10). Lymphoma occasionally involves the adrenal gland with non Hodgkin´s lymphoma which is more common than Hodgkin´s disease at this site. In a retrospective study by Paling and Williamson, 4 % of patients with non Hodgkin´s lymphoma showed evidence of adrenal metastases (11). In cases of renal cell carcinoma, the metastases in the counter-lateral adrenal gland are extremely rare (12).

The metastases are mostly discovered in patients during their follow-up carried out in consequence of their antecedent malignant disease. An occasionally, malignant disease may manifest in form of solitary metastasis in the adrenal gland in form of adrenal incidentaloma.

Metastatic affliction may be either unilateral or bilateral. Bilateral involvement is seen in 50 % of patients with lymphoma. Although bilateral metastases are more common than unilateral, in most cases they do not lead to adrenal insufficiency. The size of these secondary tumors may vary from small to huge (above 10 cm) (13).

Diagnosis

The median duration from the diagnosis of primary cancer up to the identification of adrenal metastases is approximately 2.5 years. Sagalowsky et al described a case of a solitary metastasis to the counter-lateral adrenal gland 22 years after radical nephrectomy for renal cell carcinoma (14).

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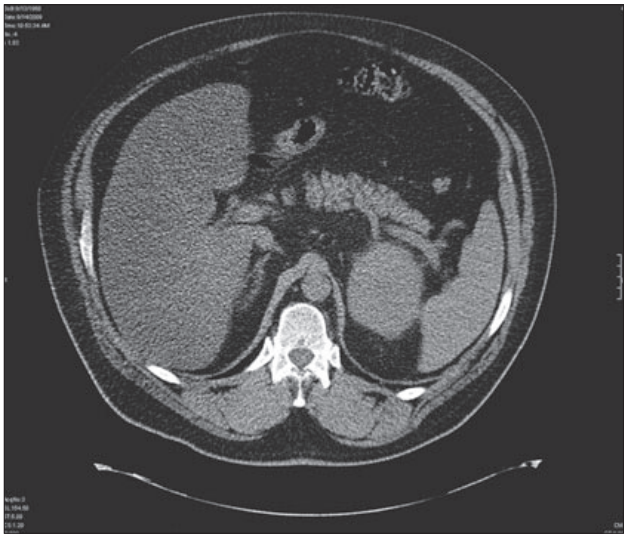

Fig. 1. CT view of metastasis of malignant melanoma into left adrenal gland. Normal CT view of right adrenal gland.

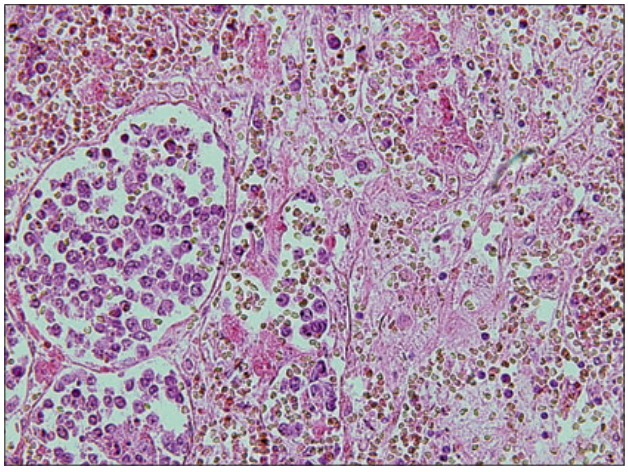

Fig. 2. Histological view of adrenal cortex with haemorrhage and collection of lymphoma cells in dilated capillaries. Hematoxylin-eosin staining, 200x (31).

In order to identify antecedent or present malignancy, particular history should be taken on every patient who by means of imaging methods is found to have adrenal incidentaloma. We inquire for weight loss, fever of unknown origin and smoking. In addition to latter inquiries, we should not forget to examine the family history of malignancies.

By physical examination, we look for the presence of lymphadenopathy, skin lesions of melanoma character, resistance in breast etc.

If by means of computed tomography (CT) or magnetic resonance, a lesion of adrenal gland is found in a patient with a known malignant disease and multiple organ dissemination, usually no further examination is necessary as it does not influence the further therapeutic process (6, 15). If oncological treatment was successfully completed and remission was induced with no signs of dissemination of the disease, further differentiation of the adrenal lesion is essential. CT and MRI with the evaluation of lesion's characteristics play the key role in differential diagnosis.

Benign adrenal masses contain abundant intracytoplasmic fat in contrast to lipid-poor malignant lesions. On unenhanced CT scan, attenuation value of <10 Hounsfield units (HU) suggests a lipid-containing benign adenoma with a specificity of more than 95 % and sensitivity of 71 %. Approximately 29 % of adenomas show an attenuation value of more than 10 HU (lipid-poor adenomas) resulting in an indeterminate finding (16). Standard contrast-enhanced CT images are obtained 60 seconds after contrast media administration. At this time the attenuation values of adenomas and metastases are nearly identical. Adenomas lose enhancement more rapidly. Masses with attenuation value of less than 30–40 HU on a contrast-enhanced CT scan obtained with a 15-minute delay are almost always adenomas. Another useful method available for differentiation between benign and malignant lesions is the calculation of the percentage of washout at 15 minutes after contrast media administration from the initial enhancement. Optimal threshold washout for adenoma is 60 % with sensitivity and specificity of 86 % and 92 %, respectively (17). Small metastases are usually homogeneous analogues of adenomas, whereas big metastases are often heterogeneous in appearance as a result of hemorrhages and necroses within the lesions. Calcifications are rare in metastases.

The intensity of signal of metastasis in T2 weighting of MRI is higher than that of benign and hormonally inactive lesions. According to several authors, faster washout of gadolinium in MRI is typical for adenomas and may distinguish them from metastatic lesions. However, other studies did not prove this relation and therefore dynamic–gadolinium MRI is not a standard method used for that purpose. The more recommended chemical-shift MRI potentially enabling to distinguish adenomas from metastases is based on a principle of difference in resonance of protons in lipids and water. The reported sensitivity and specificity results for a benign lesion were 87–100 % and 92–100 %, respectively (18, 19). The rate of diagnostic failure could be high (13–17 %) in lipid-poor adenomas. Park et al 2007 compared delayed enhanced CT and chemical shift MRI for evaluating the hyperattenuating incidental adrenal masses (>10 HU) on non-enhanced CT. Although there was no significant difference between the two imaging modalities, the delayed enhanced CT scans had higher sensitivity and specificity for lipid-poor adenoma than did the chemical-shift MR (10).

Recent studies documented the use of the contrast-enhanced doppler sonography on characterization of adrenal masses (20, 21). Friedrich-Rust et al. found an early arterial contrast enhancement and rapid washout in all patients with primary and secondary malignant lesions of adrenal gland and in only 22 % of patients with benign adrenal masses at contrast-enhanced sonography. In the diagnosis of malignant adrenal mass, the sensitivity and specificity of contrast-enhanced sonography were 100 % and 82 %, respectively (21).

^{131}I-19-Iodocholesterol scintigraphy may be helpful in differentiating the metastases with typical absence of radiumcholesterol absorbtion in adrenal mass.

^{18}F FDG – PET is another method of distinguishing metastases from benign adrenal lesions. Yun et al 2001 found a sensitivity of 93 % and specificity of 94 % when using lesion uptake higher or equal to liver uptake as a criterion for the positive result (22). The most common type of tumor to cause false positive results on FDG-PET scan is reported to be that of pheochromocytoma of the adrenal (22). Lower FDG uptake has been reported in metastases from neuroendocrine tumors (23). Jana et al founded false negative lesions on FDG-PET in patients with pulmonary carcinoid (24). On the other hand, while the inhibitor of 11beta-hydroxylase ^{11}C metomidat may distinguish adrenocortical carcinoma from metastases of tumors of noncortical origin, it is unable to differentiate between adrenal adenoma and adrenal carcinoma (25, 26).

The laboratory examination is not indicated in case of known malignancy and unilateral adrenal metastasis, however particularly in order to exclude the primary hypocortisolism, the hormonal evaluation of adrenal gland is obligatory in patients with bilateral masses of metastatic origin. In this case, the examination of serum cortisol, urinary free cortisol and serum ACTH is recommended, eventually including the ACTH test. The examination of adrenal overproduction is not necessary in case of known adrenal metastasis except for the evaluation which rules out catecholamine overproduction. Adler et al. found a surprisingly high incidence of pheochromocytomas in cancer patients. In their study of 33 patients with history of cancer who underwent resection of an adrenal lesion, nearly l of 4 patients had a pheochromocytoma rather than a metastasis or adenoma. Hypertension was the initial presenting symptom in 75 % of patients with pheochromocytoma, however 25 % of patients had neither hypertension nor any other classic symptoms of pheochromocytoma present (27). None of the clinical and radiographic parameters effectively ruled out the pheochromocytoma. Most pheochromocytomas demonstrate high-signal intensity on T2-weighted images on MRI. High signal intensity should not be used as a feature to suggest or exclude pheochromocytoma because these tumors manifest also with moderate signal intensity on T2-weighted images (28). The consequences of misdiagnosing a pheochromocytoma are grave. Screening for catecholamine overproduction should include the measurement of plasma metanephrines or 24-hour urinary metanephrines, the sensitivity of which is reported to be in range of 97–100 % (29). Tumor markers may be helpful when previous history of malignancy or malignant signs of adrenal tumor are present (25).

Adrenal biopsy is a nowadays method of relatively narrow indications and is performed mainly if the suspicion of malignant infiltration of adrenal gland by known primary oncological disease is present. Cytologic evidence of adrenal tissue excludes metastatic adrenal malignancy. Adrenal biopsy showing malignancy has a positive predictive value of 100 % and a negative predictive value for malignancy of 92 % (30). In case of bilateral masses, it may be valuable for identification of tuberculosis and other granulomatous lesions as well as of malignant lymphoma (Figs 1 and 2) (31). If the definitive diagnosis of adrenal malignancy is essential for oncological treatment, it may be performed under CT or ultrasound control. However, because of the risk of severe complications, the possibility of pheochromocytoma should be excluded first. Implantation metastases of carcinoma after percutaneous fine-needle aspiration biopsy were reported (32).

Therapy and prognosis

As written above, if the malignant disease is disseminated at the time of diagnosis of the adrenal mass, no further differentiation of lesion is necessary. If the dissemination is not present, further differentiation using imaging techniques should be performed. In case of bilateral metastases, adrenal insufficiency should be excluded in every patient. Surgical treatment is indicated in case of solitary metastases, where it may be included also in more radical procedures in order to minimize the tumor mass, i.e. debulking. Various case series documented the efficacy of transarterial chemoembolization and imaging-guided percutaneous radiofrequency ablation in local control of adrenal metastases (33, 34). The further management of patients with adrenal metastases belongs to the oncologist. The prognosis of the disease is usually very poor with average survival rate of 3 months.

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