

Adrenal Metastasis in Colon Carcinoma: Not Easy to Consider but Easy to Find

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ABSTRACT

We report herein four cases of patients with adrenal metastases of colon adenocarcinoma, adrenal metastases were quiescent in the four patients, discovered during follow-up visits of a primary cancer and these have been detected by computed tomography CT scan.

Metastatic disease was not limited only to the adrenal glands. We had a pulmonary metastases in the first case and liver metastases in the three others.

Bilateral adrenal metastases were found in one patient with an interval of time between the first ipsilateral metastasis and the second contralateral one. All patients underwent an adrenalectomy for their metastases and histologic examination confirmed colorectal origin.

Though liver and lung are the main metastatic sites, we should consider the possibility of adrenal metastases post primary colorectal cancer surgery.

Keywords: Metastatic adrenal tumor, Colon cancer, Rectum cancer, Adrenal metastases

INTRODUCTION

Adrenal metastasis most commonly occurs in patients with lung, kidney, breast, and gastrointestinal carcinomas [1-3]. However adrenal metastases from colorectal cancer are not rare in findings based on autopsy reports [4]. On the other hand the most common sites of metastases of colorectal cancer (CRC) are primarily liver and lung, followed by brain, bone metastases,[5] usually adrenal metastases are metachronous and ipsilateral and are frequent in patients with disseminated cancer.

Metastases to the adrenal gland can be detected during follow-up after primary operations or incidentally, as the so-called adrenal incidentaloma. However these lesions should not be called incidentalomas, since they are found in the context of a cancer disease [6]. Clinically, the symptoms seen in patients with disseminated carcinoma are quite similar to those caused by adrenal insufficiency secondary to extensive metastases, but such symptoms rarely appear as the initial sign of recurrence in colorectal adenocarcinoma [7].

We herein report four cases of adrenal metastases from colon and rectum cancer. In the four patients, metastases were diagnosed by computed tomography (CT scan) and confirmed by histologic examinations.

CASE REPORTS

Case 1

A 64 year old woman with no personal specific pathological history but who has her mother diagnosed with a colon cancer, underwent a left hemicolectomy for a well differentiated adenocarcinoma of the Left colon infiltrating the serous in January 2015, at that time no metastases were found in the resected lymph nodes classified PT3 N0 M0 R0, however pulmonary and adrenal nodules were detected and considered not metastatic by radiologists, postoperative course was uneventful.

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During follow up a colonoscopy and CT scan had been performed, but there was no evidence of local recurrence or metastases.

25 months after surgery a thorax and abdomen CT scan was performed, it revealed the progression of two pulmonary nodules, one right apical measuring $42 \times 43 \times 39$ mm and another one left laterobasal measuring $75 \times 61 \times 50$ mm. With a stable suprarenal mass measuring 12×8 mm, adjacent to the left adrenal gland, the right adrenal gland was normal. 8 days after, the patient underwent a left lower lung lobectomy; histologic examination confirmed the pulmonary lesion to be well differentiated adenocarcinoma similar to those of colon carcinoma resected 25 months previously.

A second thoracoabdominal CT scan revealed a stable right apical pulmonary nodule but progression of the left adrenal gland nodule measuring $32 \times 21 \times 21$ mm (**Figure 1**).

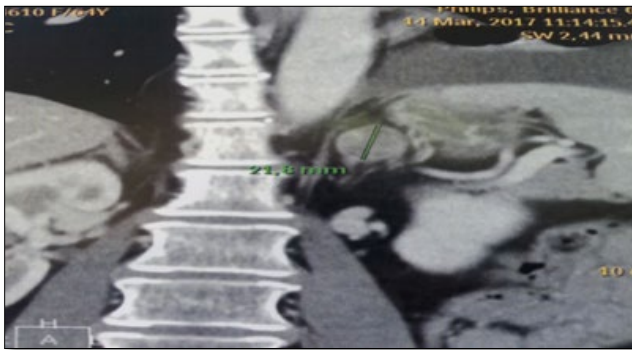


Figure 1. CT scan of case 1 demonstrating an enlarged heterogeneous left adrenal gland.

50 days after the first lung surgery, the patient underwent an upper right lobectomy, with the same histological results. The patient was discharged following an uneventful recovery and programmed for a left adrenalectomy.

Thus, left adrenalectomy was performed 35 days after, revealing a large solid mass. Macroscopically, the adrenal gland was completely replaced by tumor tissue, leaving no normal adrenal tissue remaining with no obvious renal involvement. Histologic examination confirmed the adrenal lesion to be a well-differentiated adenocarcinoma and the histologic findings were similar to those of the left colon carcinoma resected previously.

A CT scan had been conducted fifteen days later showing similar images as the first ipsilateral adrenal metastasis on the right adrenal gland. The patient underwent a second adrenalectomy for this new contralateral metastasis one month later. Histological analysis confirmed the well differentiated adenocarcinoma and its colonic origin by immunohistochemistry: CK20+, CDX2+, CK7-, mutant RAS gene. The patient then received three cycles of chemotherapy FOLFOX type and corticosteroid treatment by the endocrinologist.

Case 2

A 49 years old patient with no specific pathological history presenting anal bleeding during defecation and abdominal pain. An endoscopic examination revealed a tumor of the sigmoid. The histological examination of the biopsy revealed a moderately differentiated Invasive adenocarcinoma. The thoracic-abdominal-pelvic CT scan showed sigmoid thickening with potentially resectable liver metastases.

Operated on 01/06/2016 when she benefited from a low segmental colectomy with colorectal anastomosis, confirming the preoperative pathological examination (moderately differentiated adenocarcinoma) classified pT2N0M1 (liver metastases) and RAS gene: mutation confirmed.

The patient received 12 cycles of chemotherapy type XELIRI+BEVACIZUMAB, the evolution was marked by a partial response, three months later we decided to reoperate the patient, and she underwent a right hepatectomy with metastasectomy of the segment II.

15 months later, during regular monitoring an abdominal CT-Scan revealed a right adrenal metastatic recurrence (**Figure 2**) for which a right adrenalectomy was performed by transabdominal supra mesocolic approach, postoperative course was uneventful.

Histological examination confirmed the colic origin of the adrenal metastasis.

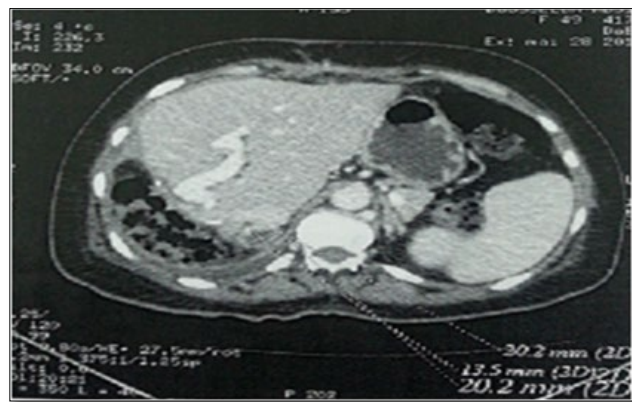


Figure 2. CT scan of case 2 demonstrating an enlarged right adrenal gland with a low density area.

Case 3

A 56 years old woman with no specific pathological history, underwent a partial left segmental colectomy for a sigmoid adenocarcinoma in April 2017, classified PT4a N1b M0 R0, with no evidence of distant metastases, postoperative course was uneventful. Patient received 8 cycles of chemotherapy, a control CT scan showed in September 2017 a liver metastasis in segment VIII of 1 cm and a right adrenal mass

with malignant characteristics (**Figure 3a**) for which a right adrenalectomy (**Figure 3c**) combined with hepatic segment VIII metastasectomy were performed 25 days after. During multidisciplinary meeting this right adrenal mass was also found on initial CT scan which has been initially considered as incidentaloma by the radiologist (**Figure 3b**).

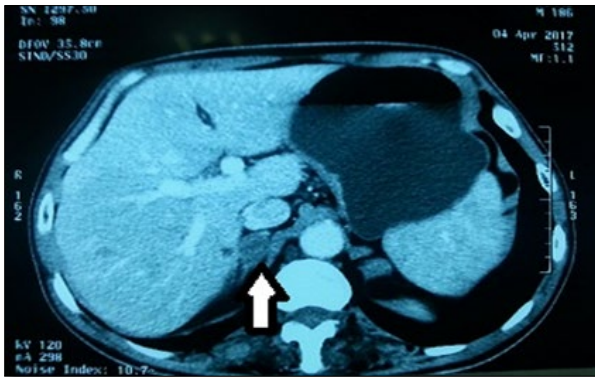


Figure 3a. Initial CT scan of case 3 demonstrating an enlarged heterogeneous right adrenal gland considered as incidentaloma.

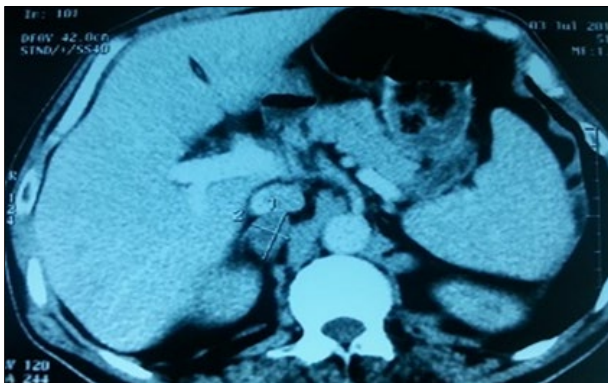


Figure 3b. CT scan of case 3 demonstrating an enlarged heterogeneous right adrenal gland.



Figure 3c. Picture demonstrating case 3's right adrenal gland resected.

Histological examination confirmed that the adrenal lesion is a well-differentiated adenocarcinoma of colic origin (**Figure 3d**).

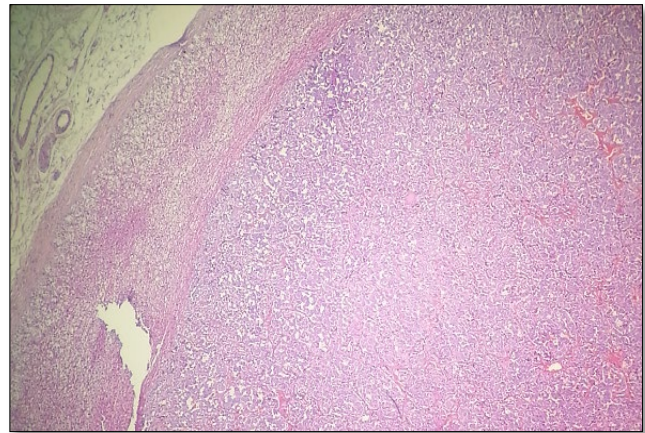


Figure 3d. Microscopic appearance of the adrenal tumor from case 3 showing a well differentiated adenocarcinoma, similar to that found in the primary colon carcinoma.

Case 4

A 60 years old woman with no significant history, presented with chief complains of weight loss, occult blood in stool. Abdominal Computed Tomography (CT) scan and colonoscopy revealed rectum adenocarcinoma with no metastases

Anterior resection with mesorectum excision was performed by laparoscopy, postoperative course was uneventful and she was discharged 6 days after. During follow-up, 4 months later a thoracic-abdominal-pelvic CT scan showed two right liver nodules with left adrenal mass of 44 × 32 mm.

Patient received 3 three cycles of chemotherapy (oxaliplatin+Xeloda) then have been operated 7 months after first primary surgery; she underwent a right hepatectomy with a left adrenalectomy by open surgery.

Histologic examination confirmed the adrenal lesion to be well differentiated adenocarcinoma similar to those of rectum carcinoma resected 7 months earlier.

DISCUSSION

The adrenal glands are frequent sites for metastases from many cancers; theoretically any primary cancer can spread to the adrenals. According to Lam and Lo [3], 90% of the metastatic lesions in the adrenal glands were carcinomas; several other studies have shown that metastases to the adrenal gland from malignant neoplasm of epithelial origin were not rare findings at autopsy [8]. However, the primary tumors most often responsible for adrenal metastases are those of lung, breast and kidney.

The incidence of adrenal metastasis found at autopsy was 8.6%-27.0% of all malignancies also based on these autopsy

studies, the incidence of metastasis to the adrenal glands from colorectal carcinoma was surprisingly not rare [1,4,8,9], since the first report of adrenal metastasis on an autopsy study in 1938, several studies show that incidence ranges are from 1.9% to 17.4%, Cedermarck et al. [10] reviewed the autopsy records of 457 patients who had died from carcinoma of the colon and rectum and found the frequency of metastasis to the liver and lung to be 48% and 38%, respectively, while those to the adrenal gland was 14%.

Novel imaging modalities and the widespread use of abdominal imaging modalities including ultrasonography, CT scan and MRI show how relatively important the incidence of adrenal metastasis is. Usually, preoperative diagnosis of adrenal metastases is arduous because adrenal metastatic lesions are not only asymptomatic but also often being mistaken for lymph node metastasis adjacent to the aorta [11].

The prevalence of a primary adrenal tumor found on a CT scan of patients being staged or followed-up for a known adrenal tumor, ranges from 0.35% to 5%. In turn, the prevalence of metastatic disease of the adrenal glands ranges from 38% to 57% [12].

Wade et al. [13] reported that 8 of 47 (17%) patients who underwent adrenalectomy for metastatic cancers had adrenal metastasis from colorectal cancer. A study on adrenal incidentaloma with MRI revealed some cases of adrenal metastasis, but unfortunately, details on the incidence of primary tumors were not submitted, despite different incidence rates among reports.

It is conceivable that adrenal metastasis from colorectal cancer is not rare. In these four reported cases adrenal metastases were found by radiological exams CT scan conducted during follow up, however by discussing case 3 and 4 during multidisciplinary meeting we found that adrenal mass already exist on initial CT scan. They were also clinically silent and there were no reason other than controlling evolution of primary and other metastases sites to search for adrenal metastases. Besides radiologic aspect another way to explore adrenal tumors is frequently used; Candel et al. [14] conducted a study on fine-needle aspiration biopsy of adrenal masses, which revealed that 5 of 39 cases (12.8%) of adrenal metastasis from malignant lesions were derived from colorectal cancer. They also highlighted how fine-needle aspiration biopsy of adrenal masses was helpful for making an accurate diagnosis. Although, this procedure was not performed preoperatively in these reported patients, it is considered effective for the differential diagnosis of adrenal masses.

As part of our literature review, adrenal metastases of colorectal cancers are mainly ipsilateral and metachronous or at least the diagnosis was made after initial surgical resection of the primary tumor. According to Chen et al. [15]

research six cases of adrenal synchronous adrenal metastases have been reported in literature, but as demonstrated in case 1 and 3 these synchronous adrenal metastases may be considered as incidentalomas while they are metastases. All adrenal metastases were quiescent. However in case of "incidentaloma" it is essential to examine whether the adrenal mass is functional or nonfunctional [16].

Usually, adrenal metastasis is thought to indicate widespread disease; Cedermarck et al. [10] reported that if patients with colorectal carcinoma show metastatic adrenal involvement, it is likely that more than two organs are involved; in these cases the four patients had other organs metastases when we discovered adrenal metastases. Lung metastases were discovered in the first case and it was liver metastases for the three others. Occasionally, an adrenal mass may be presented as a metastatic cancer of unknown primary; these tumors should generally be treated with systemic therapy based on the origin of the primary cancer.

It is acknowledged that the spread of adrenal metastases occurs via the arterial, portal venous or lymphatic routes. Hematogenous spread is the principal route of primary carcinoma metastasis to the adrenal which may explain the fact that adrenal metastases from colorectal cancer are oftenly a manifestation of systemic spread of the disease. Thus; they represent a worse medium and long-term prognosis.

Katayama et al. [17] suggested a route of hematogenous metastasis from the primary lesion via the lung to the adrenal gland, According to this theory, although in case one patient's lung metastasis became evident at the same time with the first adrenal metastasis, it is difficult to be sure which metastasis occurred first.

It is agreed that determination of the serum CEA level and its synergy have an adjunctive role in following up patients with colorectal carcinoma [18]. Serum CEA is reported to be useful for indicating the presence of adrenal metastasis after surgery for colorectal cancer [19]. However, the high serum level of CEA in these reported patients couldn't be related with certainty to adrenal metastasis especially in case one. In contrast, there have been multiple cases in which serum CEA level remains within the normal range in spite of an occurrence of adrenal metastasis [20,21].

Consequently, other modalities should be performed to evaluate the stage of colorectal cancer with accuracy, in addition to measuring serum CEA. In a series of radiological studies evaluating adrenal metastasis, ultrasonography and CT scan are most popular [22], due to their availability and their non-invasive characteristic. Recent progress, has allowed us to detect adrenal masses as small as 1 cm in diameter with a high degree of accuracy [23]. It's legitimate to think that periodic imaging controls despite CEA level are more efficient to discover adrenal metastases in early stages.

In fact adrenal metastases were once considered incurable, apart from the type of adrenal mass, surgical indication has been increasingly incriminated in the management of adrenal tumors especially by reducing the size limit to be resected. Current literature suggest lowering the absolute cut-off to 4 cm because adrenocortical carcinomas are >4 cm. In case of adrenal metastases regardless of size or any clinical or radiological or hormonal abnormalities, adrenalectomy should be considered as the first-line treatment [24]. Also if surgeon skill and lesion characteristics allow, laparoscopic adrenalectomy should be the surgical technique of choice [25,26].

Wade et al showed that adrenalectomy for metastatic carcinoma was safe, despite a projected 5 year survival rate (13%) that is significantly inferior to resections for colorectal metastases to lung (36%) or liver (26%), but superior to brain (none) [16].

In these reported cases; first patient underwent pulmonary lobectomy so we decided that laparoscopy was too risky for her due to respiratory potential complications, the second patient benefited from a right hepatectomy so local adhesions were considered as an encumbrance for laparoscopy approach, In case three posterior localizations of liver metastases was considered a hindrance of the laparoscopic approach. Also for case for where major liver surgery justified open approach. Therefore we choose open adrenalectomy for all patients.

In general it is suggested that separate metachronous metastases in bilateral adrenal glands may not achieve desired results through chemotherapy alone but surgical resection and continuous follow-up as well.

Also according to Lam and Lo [3], multidisciplinary consultation followed by careful patient discussion should allow selection of patients they are most likely to benefit from surgical treatment. In their study, surgical resection for adrenal metastasis was associated with rare mortality and low morbidity rates. It offers temporary but effective pain relief and may result in survival benefit in selected patients [27].

Many types of approaches are possible to perform adrenalectomy, in posterior adrenalectomy, many patients present a troublesome periadrenal 'reaction' which complicates the dissection and makes the space-confining posterior approach potentially hazardous. This difficulty and the need for critical assessment of the remainder of the peritoneal cavity makes the anterior approach the procedure of choice; we choose to perform the five adrenalectomies by anterior supra-mesocolic approaches in addition to its much simplified aspect, it allows in a multimetastatic patients an intraoperative exploration of all abdomen searching for other metastases sites especially intraperitoneal carcinosis.

CONCLUSION

In conclusion despite that liver and lung are the main metastatic sites the incidence of adrenal metastases from colorectal cancer is not rare in autopsy series. Therefore, adrenal metastases should be munitiously searched during the follow-up of patients who undergo a primary operation for colorectal cancer, and not considered as incidentalomas when discovered on initially extension assessment, fine needle aspiration biopsy of adrenal masses discovered on initial imaging can specify metastatic nature of these so called incidentalomas.

INTEREST DECLARATION

Authors declare no conflict of interest.

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