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Nonfunctioning Adrenocortical Carcinoma: A Review of The Lesser Known Facts

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ABSTRACT

Adrenocortical carcinoma is an extremely rare tumour and by tradition is classified as functioning and non-functioning. It has been suggested that this differentiation may be misleading and may not reflect true state of tumours; thus rendering this charade redundant in modern times. Non-functioning tumours are even rarer and present with a wide variation in the clinical presentation requiring high suspicion for diagnosis. Non-functioning tumours commonly present as incidentalomas or clinically apparent masses and an early diagnosis becomes crucial in complete cure. The article, supported with extensive literature research, focusses on putting light over various enigmatic aspects of this rare tumour and stresses on its lesser known facts.

Keywords: Adrenocortical carcinoma, Non-functioning tumours, Incidentalomas, Lesser known facts

INTRODUCTION

Adrenocortical carcinoma (ACC) is an extremely rare tumour having an incidence of only two cases per million while that of non-functioning adrenocortical carcinoma (NACC) can be estimated to be up to 0.6 cases per million persons annually [1]. ACCs may present either as incidentalomas or as clinically apparent carcinoma. Prevalence of incidentaloma is estimated to be up to 4.4% in computerised tomography and 6% in autopsy series [2-4]. ACC can further be classified as functioning and non-functioning depending on the hypersecretion of the adrenal gland. Non-functioning ACC usually have a poorer prognosis due to the delay in diagnosis [5]. The aim of this review article is to discuss presenting features, diagnostic modalities, evaluation, prognosis and treatment of non-functioning adrenocortical carcinoma with comprehensive review of literature. It also highlights the lesser known presentations of the tumour.

MATERIALS & METHODS

Literature review was comprehensively carried out in the following databases: Medline (via pubmed), Embase, the Cochrane Central register of Controlled Trials (Cochrane Library), to screen published articles reporting non-functioning adrenocortical carcinoma. Following Medical Subject Headings (MeSH) search terms were used: "non-functioning adrenocortical carcinoma" OR "advanced adrenocortical carcinoma". After comprehensive data screening, the lesser discussed facts were highlighted and compiled in the article. Reference lists of all related articles and published abstracts from authoritative academic conferences were checked.

PRESENTING FEATURES

NACC shows a bimodal age distribution with the first peak occurring before age 5 years and the second peak in the fourth to fifth decade of life [6,7]. A predominant incidence in young females was noted in functioning ACC while higher incidence of NACC in older males was noted by Lipsett et al. [8]. Most of the studies suggest left sided prevalence, however a few also mention right sided preponderance [9-15]. According to Favia et al. and Sidhu et al. [2,5], size of tumour at presentation may range from 3.5cm to 20cm (median 8cm) with no significant difference between functioning and non-functioning groups. Malignant status in a tumour of size 1.5-6 cm is very slim (<0.03%)

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while it goes up to 15% in tumors greater than 6 cm size as per Khafagi et al. and McLeod et al. [16,17] and 35-98% as per Ross et al. [18]. The time from initial presentation to diagnosis shows a wide range in various studies from 1 to 13 months (median 5 months) as per Barzon et al. [3] to 0 to 53 months (median 8.7 months) as per Luton et al. [19].

NACC usually shows a variety of symptoms in patients most commonly abdominal pain (90%), associated fever and fatigue (30%), profuse sweats (20%), hypertension (20%), loss of weight (20%), weakness, pain, indigestion, nausea and vomiting [10,20] while in asymptomatic patients it is mostly found during sonography incidentally [3]. Less common manifestations include hematuria, left varicocele and dyspnea [10]. Due to large size of tumor at diagnosis, a significant number of patients present with an abdominal mass or may also present with symptoms of metastatic disease (58%) like pathologic fractures, bone pain etc. [13,21,22]. Tumor spreads most commonly to lung (67%), liver (52%) and bone (32%). Metastases may be non-functioning even though from a primary functioning tumor [22]. Large lesions may present with fever of unknown origin due to central tumoral necrosis in many cases [23]. Other unusual manifestations include lower extremity edema, urinary obstruction and Budd-Chiari syndrome [24]. Besides, it can also present along with breast carcinoma, osteosarcoma, brain tumors (Li-Fraumeni syndrome) [25].

A delay in diagnosis is majorly attributable to:

- Asymptomatic presentation in many cases.
- Insidious nature of symptoms [25].
- Absence of a systemic inflammatory response syndrome even with large tumor burden [26].

BIOCHEMICAL ANALYSIS

NACCs are called so owing to the absence of biochemical excess of hormones and their clinical effects on the patient. This absence may be a consequence of the following: (a) formed precursors have no hormonal activity, (b) produced compounds are inactive, (c) insufficient amounts produced, (d) true non-functioning tumors unable to form steroids, [23] (e) camouflaging under normal physiology (virilising tumors in men and feminizing tumors in females). It is because of this wide spectrum of possibilities of a nonfunctioning tumor, that, measurement of basal secretion and excretion of corticosteroids (8 a.m. and 6 p.m.), low dose (1 mg overnight or 2 mg/day for 2 days) and high dose (8 mg/day for 2 days) , dexamethasone testing, metyrapone, and ACTH and 24 h precursor steroid excretion with 17-hydroxyprogesterone and its metabolites, supine and upright plasma renin activity and plasma aldosterone should be performed in patients with apparently clinically non-functioning tumours [22,23]. The most common steroids assayed are 24 h urinary excretion of 17-KS and 17-OHCS, and plasma DHEA and DHEA-S [24]. A surprising phenomenon has been reported by Bradley et al. and Didolkar et al. [23] which shows conversion of initially nonfunctioning tumors into functioning ones late in the course of disease, thus proving differentiation based on functionality redundant [23].

RADIOLOGICAL INVESTIGATIONS

Imaging is the key to diagnosing adrenal carcinoma. Ultrasonography of the adrenal gland can prove to be very effective for screening purposes but is limited by operator skills and patient body habitus [27,28]. It can identify displacement of surrounding structures caused by the tumor. A thin collimation computerized tomography(CT) is considered diagnostic method of choice. Nodules as small as 3 to 5 mm can be identified in CT with clear visualization of retroperitoneum and perirenal fat. It can also be used to identify malignant lesions and distant metastasis as per many studies [24]. Magnetic resonance imaging(MRI) is superior to CT in terms of identification of tumor thrombosis especially in inferior vena cava, adrenal and renal veins and for distinction between primary malignant ACCs, non-functioning adenomas and pheochromocytomas [29-31]. Other investigations play a supportive role in the diagnosis and are scintigraphy with iodocholesterol scanning (to identify functioning of masses) [32], venography, selective arteriography (distinguish adrenal masses from upper pole renal tumors) [24] 18-F Fluorodeoxyglucose positron emission tomography (18-F-FDG-PET) can very well be used to distinguish malignant lesions from benign ones and to detect metastases according to multiple studies [33-36]. 11-C-metomidate PET is successfully used to detect non-necrotic ACCs [37]. Fine needle aspiration/ cut biopsy is not usually done as it poses a high risk of needle tract metastases [38]. Intravenous pyelography, retroperitoneal pneumography, nephrotomography have only historic significance and have been largely replaced by CT [23,25].

PREOPERATIVE PREPARATION

After imaging studies, if the adrenal tumor is deemed resectable contralateral kidney function has to be assessed by evaluation of serum creatinine levels and normal anatomy and dye excretion on CT; as the tumor may invade the adjacent kidney and its vasculature, thus requiring its removal. Administration of hydrocortisone is done preoperatively as the contralateral adrenal gland may be suppressed. Mitotane causes partial regression of primary tumor and metastases. Ketoconazole (400 mg/day) blocks the synthesis of steroids. Metyrapone and Aminoglutethimide are other agents used. Low molecular weight heparin for prophylaxis against thromboembolism is effective [25].

TREATMENT

Surgery is the mainstay of treatment in tumors larger than 4 cm (3 cm as per Thompson et al), suspicious CT appearance (malignant) or functioning masses. Also, patients having an

increase in size of the adrenal mass (>1 cm) or hormonal dysfunction should be considered for surgery [39-42]. Masses not satisfying this criterion can be observed with CT scan. In many series it is proved beyond doubt that open approach is best suited for a case of presumable ACC due to risk of tumor capsule violation, tumor fragmentation and the potential difficulty in performing R0 resection [25,43,44]. Anterior abdominal approach (midline, bilateral subcostal, flank or thoracoabdominal incisions) is better than posterior as it allows full staging and resection of the contiguous organs involved [25]. Completeness of resection may be achieved by en bloc excision of kidney, spleen, partial hepatectomy or distal pancreatectomy [21]. Lymphadenectomy along the aorta and vena cava should be done [23,26]. The presence of a tumor thrombus in renal vein, inferior vena cava or even right atrium does not preclude a complete resection and warrants cardiopulmonary bypass for complete excision of tumor and segmental vena caval resection when required [25,45-47]. In regard to tumours that are not surgically resectable or produce a clinical syndrome (pressure effects or endocrine abnormalities), maximum debulking may be of advantage [23]. However, contradictory school of thought is also present.[15]Role of mitotane (a derivative of DDT causing adrenal suppression) as adjuvant therapy for NACC is controversial and may not help in disease free interval or survival [9,13,48-50]. NACCs are observed to be radioresistant [8,24,51,52]; however external beam radiotherapy has an established role in bony metastasis [53].

SURVIVAL & RECURRENCE

Survival is seen to be negatively affected by extensive spread of disease(stage) and tumor size (>12 cm) while age, gender, endocrine functionality and mitotic index do not seem to affect it [5,22,26]. Median survival is seen to be 28 months in women and 24.5 months in men according to Favia et al. while it is 16 months as per Barzon et al. [5,22]. Linda et al. [24] mentioned that unresectable tumors have median survival of 3 to 9 months, whereas after complete resection it is 13 to 28 months .

Recurrence is seen in 35% cases having undergone apparently curative resections; thus, proving existence of micro metastasis in early phase of disease [22]. Recurrence is seen to occur in the form of locoregional disease (>65%) or isolated hepatic and pulmonary metastasis [5]. Surgical resection of recurrent disease is associated with prolonged survival [54]. Thermoablation has shown successful outcomes against recurrent or metastatic ACC [55].

FUTURE DIRECTIONS & ADVANCES

A comprehensive management protocol is hard to design owing to the low incidence of the tumor. A well harmonized 'World Registry' may prove to be extremely beneficial in reporting of substantial number of cases for better understanding [26]. Trans-arterial chemoembolization (TACE) has proved to be beneficial in reducing tumor burden associated with liver metastasis [56]. Immunotherapy is gaining popularity in recent times with PD1/PDL1 pathway directed therapy showing longer postoperative survival [57]. Yttrium-90 microsphere selective internal radiation therapy (SIRT) is understudied but has shown to be of value in second line treatment of advanced tumors after first line debulking surgery and chemotherapy [58].

CONCLUSION

It can be concluded from above discussion that NACCs are rare and aggressive tumors with varied clinical presentations requiring high suspicion for diagnosis. The classification based on functionality becomes superfluous and may suggest unnecessary differences in therapeutic approach. Hence, a full battery of hormonal assays should be used to evaluate all patients of ACC. Open approach surgery is the mainstay of treatment and should not be delayed in a patient satisfying the criteria mentioned above. Rate of surgical cure is low and thus; patients should be followed up with urinary steroid assays to detect recurrence early. Use of chemoradiotherapy for treatment of recurrence needs further prospective study.

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