Tips to facilitate a preoperative diagnosis of adrenal ganglioneuroma. Report of a challenging experience and review of the literature

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AIM: Ganglioneuroma (GN) is the most uncommon and the most benign tumor among neuroblastic neoplasms, and in 29.7% of cases it finds in an adrenal gland. Usually asymptomatic, this tumor is detected incidentally in the majority of cases. It is generally challenging to obtain a precise diagnosis of adrenal ganglioneuroma (AGN) before surgery. Misdiagnosis rate of AGN on CT and MRI is 64.7% and clinicians and surgeons are often lacking in knowledge of this rare disease. For this reason, we pointed out the clinical, biochemical, radiologic and pathologic features of AGN in our experience, with the aim to find out if there are some features able to facilitate a preoperative diagnosis. The present article also includes a review of the relevant literature in order to compare laparoscopic versus open adrenalectomy.

CASE REPORT: Right AGN in a 42-year-old woman, in whom preoperative diagnosis was very difficult and only histopathologic studies of the surgical specimen established the exact diagnosis. The patient underwent bilateral subcostal laparotomy for a large mass (sized measuring 14.5 x 11.6 x 6.5 cm.) and a right adrenalectomy was performed. Postoperative recovery was uneventful and the patient, at 12-months follow-up, is disease-free and in good health.

DISCUSSION / CONCLUSIONS: Authors stress the importance of interdisciplinary collaboration between surgeons, radiologists and endocrinologists to optimize clinical management and surgical indications. Careful evaluation by endocrine examinations and multiple imaging procedures are necessary to provide a differential diagnosis. Surgeons should consider a diagnosis of AGN in case of: 1) an adrenal incidentaloma; 2) a nonfunctioning tumor with no elevated hormonal secretions, in which compressive symptoms may occur; 3) a homogeneous, encapsulated mass, with well-defined edges, without invasion of nearby structures (no vascular involvement), with presence of calcifications and nonenhanced attenuation of <40 HU on CT; 4) a homogeneous hypointense adrenal mass on T1-weighted MRI, a heterogeneous hyperintense mass on T2-weighted MRI and a poor delayed enhancement on dynamic MRI; a SUV level on PET less than 3.0. Nevertheless, diagnosis of AGN can be extremely challenging and can only be achieved by means of histology. Treatment is complete surgical resection without the need for chemotherapy or radiotherapy. Laparoscopic adrenalectomy is contraindicated in the presence of local infiltration or tumor greater than 12 cm. Even if AGN has an excellent prognosis and recurrences are rare after surgical resections, long-term follow-up is recommended.

KEY WORDS: Adrenal gland, Adrenal ganglioneuroma, Laparoscopic adrenalectomy, Open adrenalectomy.

Introduction

Among the neuroblastic neoplasms, ganglioneuroma (GN) is the most uncommon and the most benign. GN, arising in primary sympathetic neurons of the neural crest, consists of mature ganglion cells and Schwann cells in a fibrous stroma. GN occurs in adrenal glands in
This tumor is usually asymptomatic and is detected incidentally in the majority of cases. The routine use of ultrasonography (US) and computed tomography (CT) has increased the frequency of finding of adrenal incidentalomas, which prevalence is 0.2% in young patients, 3% in people over 50 years of age and reaches 7% in those over 70 years of age. However, misdiagnosis rate of adrenal ganglioneuroma (AGN) on CT and magnetic resonance imaging (MRI) is 64.7% and clinicians and surgeons are often lacking in knowledge of this rare disease. Therefore, it is generally challenging to obtain a precise diagnosis of AGN before surgery.

We report a case of right AGN in a 42-year-old woman, in whom preoperative diagnosis was very difficult and only histopathological studies of the surgical specimen established the exact diagnosis. For this reason, we reconsider here the clinical, biochemical, radiologic and pathologic features of our AGN, with the aim to examine if come out some tips to facilitate diagnosis. The present article also includes a review of the relevant literature in order to compare laparoscopic versus open adrenalectomy.

**Case Report**

A 42-year-old woman, with no previous comorbidities, was admitted to our hospital in October 2014. She presented non-specific abdominal discomfort for about a month. Because of her symptoms, an abdominal US was performed and showed a well-defined, oval mass measuring 12x8 cm at her right adrenal gland. The patient was referred to the endocrinology department to work-up a right adrenal incidentaloma. Upon specific questioning, she reported no constitutional symptoms or showed evidence of hypercortisolism (central obesity, striae, muscle weakness, bruising, hirsutism, acne), of hyperandrogenism or hyperaldosteronism (high blood pressure, nocturia, urinary frequency, polydipsia) or crises suggesting pheochromocytoma. A physical examination revealed no signs and the results of routine laboratory tests were all found within the normal ranges. The results of tests in 24-h urine were normal. The results of plasma hormone tests were as follows: testosterone, 1.60 nmol/L (0.380-1.97); 17-OH-progesterone, 1.45 ng/mL (0.7-3.1); ACTH, 14.40 pg/mL (10-90); cortisol, 185 nmol/L (50-350); renin, 8.1 pg/mL (1.8-59.4); aldosterone, 243 pg/mL (35-310); DHEAS, 41 ug/dL (61-511). Tumoral markers: CEA, 1.0 ng/mL (<6.00); AFP, 1.01 UI/mL (<8.00); CA 19.9, 8.2 U/mL (<39.00); TPA, 69.0 UI/L (<100.00); CA 72.4, 0.93 U/mL (<5.00).

Total body CT scan detected a voluminous solid mass of 13 x 10 cm in size, with heterogeneous density (range: 40-60 Hounsfield Units) (HU), arising from right adrenal gland (Fig. 1). The tumor was adjacent to the medial side of the right lobe of the liver, to the right diaphragmatic pillar and imprinted the upper pole of the right kidney without any infiltrative aspects towards these structures. The mass extended behind inferior vena cava.

![Fig. 1: Total body CT scan detected a voluminous solid mass of 13 x 10 cm in size, with heterogeneous density (range: 40-60 HU), arising from right adrenal gland. The tumor was adjacent to the medial side of the right lobe of the liver, to the right diaphragmatic pillar and imprinted the upper pole of the right kidney without any infiltrative aspects towards these structures. The mass extended behind inferior vena cava.](image1)

![Fig. 2: Histopathological studies of the surgical specimen established the final diagnosis of mature adrenal ganglioneuroma. Macroscopic examination identified an encapsulated mass (sized measuring 14.5 x 11.6 x 6.5 cm.).](image2)

Histopathological studies of the surgical specimen established the final diagnosis of mature adrenal ganglioneuroma.
A MRI was performed to characterize vertebral lesions, but this imaging test was inconclusive. The role of PET-TC was discriminant, showing heterogeneous FDG uptake in right adrenal gland with a standardized uptake value (SUV) of max. 4.2, suggesting for a mild glucometabolic activity lesion. Finally, osteoblastic lesions were not metabolically active.

The patient underwent bilateral subcostal laparotomy and a right adrenalectomy was performed. The lesion was completely excised. Postoperative recovery was uneventful and the patient was discharged on the 7th post-operative day. Histopathological studies of the surgical specimen established the final diagnosis of mature AGN. Macroscopic examination identified an encapsulated mass (sized measuring 14.5 x 11.6 x 6.5 cm.) (Fig. 2) with a firm consistency and a solid, yellowish-white cut surface, without areas of necrosis or hemorrhage. On the surface of section, residual adrenal parenchyma (of the size of 2.5 x 1.2 x 0.4 cm.) was detected. Microscopic examination revealed mature ganglion cells among a fibrous stroma. Not observed nuclear atypia, mitosis or necrosis (Figs. 3, 4). Immunohistochemical analysis showed positivity for S-100 protein, VIP, Sinaptophysin and negativity for Chromogranin A (Figs. 5, 6).

At 12-month follow-up, the patient is disease-free and in good health.

**Discussion**

GN are fully differentiated benign tumors that are most commonly located in the sympathetic trunk in the pos-
terior mediastinum and retroperitoneal regions. Only 29.7% occur in the adrenal gland, 21.8% in mediastinum, 20.8% in retroperitoneum and 10.9% in cervical region. Other rare locations include heart, bowel, bone and parapharyngeal region.

Hypothesis for the pathogenesis of GN includes the induced maturation of neuroblasts in a neuroblastoma into distinct ganglion cells, the separation of the remaining cells from embryonic neural crest and the necrosis of neuroblasts at an early stage of tumor development. The macroscopic characteristics of AGN are an encapsulated mass with a firm consistency and a solid, homogeneous, greyish-white cut surface. Histopathological examinations show mature ganglion cells and Schwann cells among a fibrous stroma. They can be classified in two main groups: the mature type, that is composed of mature Schwann cells, ganglion cells and perineural cells; the maturing type consists of cells with different maturation levels, ranging from mature cells to neuroblasts with a similar stroma. According to immunohistochemical analysis, AGN are characterized by reactivity for S-100, vimentin, synaptophysin and neuronal markers.

The mean ages at diagnosis for patients with AGN are 31, 39.2, 49 and 50 years from series reported respectively in Texas, China, Canada and Greece (7). The tumor similarly affects males and females (1.13 : 1). AGN are slow growing lesions, usually asymptomatic. When symptomatic, they present with nonspecific symptoms (as in the case of our patient) related to their size or location with compression of neighboring structures. Although these tumors are most commonly non-functional lesions, it has been reported that GN are secretory in up to 39% of patients releasing catecholamine. Catecholamine secretion is expected in pheochromocytoma/GN composite tumors. Therefore, all patients with an adrenal mass should undergo a careful endocrine work-up to determine whether it is functioning or not. Hormonal screening tests are performed for hypercorticoidism, pheochromocytoma and hyperaldosteronism. Cushings syndrome (urinary free cortisol, late-night salivary cortisol, and 1mg overnight dexamethasone suppression test) and pheochromocytoma (urinary catecholamines and metanephrines) should always be excluded. If there is hypertension, screening for primary hyperaldosteronism is also mandatory (plasma aldosterone/renin ratio). Laboratory measurements include total and 24-hour urinary free cortisol, ACTH, renin, aldosterone, VIP, C-peptide, somatomedin C, LH, FSH, DHEA-s, total and free testosterone, prolactin, catecholamines and their metabolites in plasma and urine, chromogranin A, gastrin, glucagon and vanillylmandelic acid (VMA).

AGN are not usually associated with genetic abnormalities. The association of AGN with hereditary multiple endocrine neoplasia syndromes is exceptional, but a genetic analysis of RET or VHL should be considered in patients with AGN when they are combined with cutaneous stigmata or other tumors more classically associated with such syndromes (pheochromocytoma, medullary thyroid carcinoma or pancreatic neuroendocrine tumor). Spinelli et al. reported that for all 14 patients (100%) the diagnosis was incidental. The patients underwent instrumental exams for different reasons and in all cases the first view of the tumor occurred during an US exam, as in our case. Symptoms as abdominal or back pain may occur in 12-33% of cases, depending on the size and the location of the mass.

In a review of the clinical, radiographic and pathologic features of 27 patients with AGN, seen at a single institution over a 20-year period, Shaya et al. confirm that AGN can mimic primary or secondary adrenal neoplasia, although AGN often have clinical and radiographic features that can help distinguish them from other adrenal tumors. US usually shows a homogeneous, hypoechoic, well-defined mass. However, CT and MRI are performed to define the size, location, composition of the mass and its relationship with adjacent structures.

On CT AGN appears as a well-defined mass, that is oval or lobulated, with a fibrous capsule, that tends to surround major blood vessels without compression or occlusion, without invading nearby structures. AGN presents low homogeneous attenuation on unenhanced CT and has a median density of 32.5 HU (range 25 to 46 HU); on postcontrast venous-phase imaging it has a median of 40 HU (range 27 to 114 HU). On delayed-phase post-contrast imaging AGN has progressive enhancement with a median density of 66.5 HU (range 38 to 104 HU). CT allows for an accurate description of the lesion and its relationship with vascular structures. Calcifications, typically fine and punctate, occur in 42-60% of cases. However, calcifications were not present in the mass of our patient on CT-scan.

On MRI, AGN usually demonstrate a hypo-intense signal on T1-weighted images, a heterogeneous hyperintense signal on T2-weighted images and poor delayed enhancement on dynamic MRI. Nevertheless, CT scan and MRI can not distinguish AGN from other tumors, such neuroblastomas or pheochromocytomas. The 18F-labeled fluoro-2-deoxyglucose positron emission tomography (FDG-PET) may help distinguish between adrenal carcinoma and AGN, based on the lowest standard uptake value. PET-CT is increasingly used in the study of adrenal incidentalomas, and in our case it was very helpful. PET scans can help complete the picture obtained by CT and MRI when making a differential diagnosis between AGN and adrenocortical carcinoma (ACC) or metastasis. Mackie et al. reported that all cases of ACC had a standardized uptake value (SUV) of 3.0 or higher, and the sensitivity and specificity to distinguish ACC from adenoma were 100% and 98% respectively.
another review in patients with AGN the SUVs were between 1.5 and 2.9. 12.

In our patient, because of the large size and heterogeneity of the mass made us suspected malignancy, and therefore we performed a PET scan prior to the surgery. PET showed heterogeneous FDG uptake in right adrenal gland with a SUV of max. 4.2, suggesting for a mild glucometabolic activity lesion (according to the radiologists). Osteoblastic lesions were not metabolically active. Therefore, PET was decisive to rule out bone metastases. However, a SUV of max. 4.2 is a high value for AGN in comparison to the reference ranges mentioned in the literature.

The treatment of any adrenal mass > 6 cm. or smaller but progressive growth, demonstrated in repeated imaging tests is unilateral adrenalectomy, after full functionality studies. Due to its minimally invasive nature, laparoscopy may be a more suitable approach to treat AGNs compared with traditional open abdominal surgery. Laparoscopic procedures are associated with decreased hospitalization time; less operative blood loss; less postoperative discomfort, pain and need for analgesics; faster postoperative recovery; earlier return to everyday activities and diet; lower overall costs. All AGN patients should undergo an open or laparoscopic adrenalectomy, depending upon detailed analysis of individual criteria, taking into consideration the tumor location, function and distance to neighboring organs or blood vessels.

In a study of Zhou et al., 13 the authors reported that open surgery was performed in patients with blood loss of > 800 ml and a violent fluctuation in intra-operative blood pressure.

Zografos et al. 14 highlighted the technical aspects and results of laparoscopic surgery for adrenal tumors > 8 cm., to determine the feasibility and safety of the procedure. They concluded that laparoscopic adrenalectomy can be considered the treatment of choice for all benign adrenal tumors up to 12 cm. to 14 cm. in size. Morbidity, mortality and hospital stay is similar, irrespective of tumor size, but experience in both laparoscopic and adrenal surgery is necessary. Large tumors suspected of being a primary malignancy based on imaging characteristics should be approached with the open technique from the start. According to the authors, the interpretation of radiologic characteristics is a cornerstone of preoperative assessment of large adrenal masses. CT may be associated with approximately a 40% underestimation of adrenal tumor size compared with the actual size determined in the histological examination. The sole widely accepted absolute contraindication for minimally invasive techniques in adrenal lesions is the presence of large primary carcinomas with or without local invasion of nearby structures and/or metastasis to periaortic lymph nodes. Large but well-encapsulated metastatic adrenal masses without evidence of local invasion can be removed laparoscopically, whereas giant benign tumors or tumors >12 cm. to 14 cm. are not an indication for the laparoscopic technique.

In their study Elfenbein et al. 15 presented an analysis of laparoscopic versus open adrenalectomy. A total of 3100 patients, having adrenal gland pathology, were identified in the 2005-2010. Of these 644 (20.8%) underwent open resection, whereas the remaining 2456 (79.2%) underwent a laparoscopic approach. Among patients who underwent open resections, 37.6% had a malignant lesion versus 19.5% in the laparoscopic group (P < 0.01). There was no statistically significant difference in 30-d mortality between the open and laparoscopic groups (1.1% versus 0.4%, P = 0.48), but there was significantly higher 30-d postoperative morbidity in the open group (13.8% versus 6.4%, P < 0.01). Median postoperative length of stay was also significantly longer in the open group (5 versus 2 d, P < 0.01). The Authors concluded that it is important to continually monitor outcomes to be sure that we are providing better quality and not just smaller incisions. The current recommendations for large (> 10 cm.), malignant adrenocortical cancers remains open, en bloc excision of the tumor and involved organs with maintenance of the tumor capsule.

Pomar et al. 16 underline that the learning curve is demanding in laparoscopic adrenalectomy. Their criteria to indicate this procedure in a benign mass are the size equal or less than 10 cm. There is no scientific consensus for the malignant adrenal tumors. Although it could be treated with laparoscopic approach to the principles of oncological surgery, this kind of diseases requires a highly selective indications. Large tumors may impede intraoperative management, increasing the risk of tearing the tumor capsule and intraabdominal tumor spread wide. The characteristics of these masses requires larger operative times and higher conversion rates. Laparoscopic approach is contraindicated in the presence of local infiltration or tumor greater than 12 cm.

Abraham et al. 17 reported a case of large AGN measuring 17 x 11 x 7.5 cm that was removed completely by the laparoscopic approach. They concluded that laparoscopic removal of large benign, nonfunctioning adrenal tumor is possible with minimal morbidity, however requires expertise in advanced laparoscopy. Nevertheless, the remarkable spread of laparoscopic techniques has in the past 10 years lead many endocrinologists to refer patients not to endocrine surgeons but to skilled laparoscopic surgeons. Endocrine surgery units remains the best setting to evaluate and treat the adrenal gland surgical pathology. 18

Due to its benign nature, AGNs rarely metastasize to the regional lymph nodes or distant organs and recurrence is rare following surgical resection. Prognosis of AGN after surgery appears to be excellent and no further therapy is necessary.
Conclusions

In conclusion, we stress the importance of interdisciplinary collaboration between surgeons, radiologists and endocrinologists to optimize clinical management and surgical indications. Careful evaluation by endocrine examinations and multiple imaging procedures are necessary to provide a differential diagnosis. Some clinical, biological and radiological features should lead the surgeon to consider a diagnosis of AGN in case of: 1) an adrenal incidentaloma; 2) a nonfunctioning tumor with no elevated hormonal secretions (rare secretions of catecholamine, vasoactive polypeptide and androgens), in which compressive symptoms may occur; 3) a homogeneous, encapsulated mass, with well-defined edges, without invasion of nearby structures (no vascular involvement), with presence of calcifications and nonenhanced attenuation of < 40 HU on CT; 4) a homogeneous hypointense adrenal mass on T1-weighted MRI, a heterogeneous hyperintense mass on T2-weighted MRI and poor delayed enhancement on dynamic MRI; 5) a SUV level on PET less than 3.0.

Nevertheless, it is still common for AGNs to be misdiagnosed. Diagnosis can be extremely challenging and can only be achieved at the end by means of histology. Treatment is complete surgical resection without the need for chemotherapy or radiotherapy because of the benign nature of lesion. Laparoscopic removal of large benign, non-functioning adrenal tumor is possible with minimal morbidity, however requires expertise in advanced laparoscopy. Large tumors suspected of being a primary malignancy based on imaging characteristics should be approached with the open technique from the start. Laparoscopic adrenalectomy is contra-indicated in the presence of local infiltration or tumor greater than 12 cm. Even if AGN has an excellent prognosis and recurrences are rare after surgical resections, long-term follow-up is recommended.

Riassunto

OBIETTIVO: Il ganglioneuroma (GN) è il tumore più raro e benigno tra le neoplasie neuroblastiche. Insorge nelle ghiandole surrenali nel 29,7% dei casi. Solitamente asintomatico, questo tumore viene rilevato incidentalmente nella maggior parte dei casi. È generalmente difficile ottenere una diagnosi precisa di GN del surrene pre-operatoriamente ed il tasso di diagnosi errata alla TC ed alla RMN è del 64,7% e medici e chirurghi sono spesso poco informati su questa rara patologia. Per questo motivo, abbiamo sottolineato le caratteristiche cliniche, biocliniche, radiologiche ed anatomico-patologiche del GN del surrene, con l’obiettivo di esaminare se esistano alcuni suggerimenti per migliorare la diagnosi pre-operatoria. Inoltre, abbiamo effettuato una revisione accurata della letteratura allo scopo di comparare la surrenec tomia “open” versus laparoscopica.

CASO CLINICO: Gli Autori riportano un caso di GN del surrene destro in una donna di 42 anni, in cui la diagnosi pre-operatoria è risultata difficile e controversa e solo mediante gli esami istopatologici sul pezzo operatorio si è giunti alla diagnosi esatta. La paziente è stata sottoposta a surrenec tomia destra per via laparotonica per una voluminosa neoformazione (dimensioni 14,5 x 11,6 x 6,5 cm.). Il decorso post-operatorio è stato regolare e la paziente, ad un follow-up di 12 mesi, è libera da malattia ed è in ottime condizioni cliniche.

DIRESSIONE/CONCLUSIONI: Gli Autori sottolineano l’importanza della collaborazione interdisciplinare tra chirurghi, radiologi ed endocrinologi per ottimizzare la gestione clinica e le indicazioni chirurgiche. Per fornire una diagnosi differenziale, sono necessarie un’attenta valutazione degli esami endocrinologici e delle procedure di “imaging”. I chirurghi dovrebberoprendere in considerazione la diagnosi di GN del surrene in caso di: 1) un incidentaloma surrenalico; 2) un tumore non funzionante, che può manifestarsi con sintomi da compressione; 3) una massa capsulata, omogenea, a margini ben definiti, che non determina invasione delle strutture contiguous (senza coinvolgimento vascolare), con la presenza di calcificazioni e attenuazione non enhanced di <40 HU alla TC; 4) una massa surrenalica che alla RMN risulta su T1 ipointesa ed omogenea e su T2 iperintensa ed eterogenea; un livello di SUV alla PET < di 3,0. Ciò nonostante, la diagnosi di GN può risultare estremamente impegnativa e può essere raggiunta solo mediante esame istologico. Il trattamento chirurgico consiste nella surrenectomia e non necessita di chemio o radioterapia adiuvante. La surrenectomia laparoscopica è controindicata in caso di infiltrazione locale o quando la neoplasia è maggiore di 12 cm. Nonostante il GN del surrene abbia una prognosi eccellente e le recidive siano rare, si consiglia comunque un follow-up a lungo termine.

References


