Adrenal incidentalomas and subclinical Cushing syndrome: indications to surgery and results in a series of 26 laparoscopic adrenalectomies

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BACKGROUND: *Casual detection of an adrenal mass, the so called incidentaloma (AI) requires an in-depth analysis of imaging phenotype together with hormonal investigation, in order to evaluate both its potential malignancy and the occurrence of a preclinical condition of hypercortisolism (Subclinical Cushing Syndrome, SCS). Aim of the present work is to evaluate surgical indications and results of surgery in patients harbouring an AI with inapparent hypercortisolism.*
METHODS: *The study has been carried on in a series of 26 Laparoscopic Adrenalectomies (LA) performed from January 2009 and January 2015. Indications to surgery included AI (11 cases), Cushing's syndrome (7 cases), suspected metastases (5 cases) and Conn's disease (3 cases). Six patients with AI had a SCS associated with variable forms of a metabolic syndrome: they were evaluated in detail analysing cortisol secretion and values of Arterial Hypertension, Diabetes Mellitus and BMI before and after surgery.*
RESULTS: *As far as SCS is concerned, LA was completed in 5 patients (one case converted). Pathology revealed 5 adenomas and one nodular hyperplasia. Four cases required oral cortisone administration at the discharge. At a mean follow-up of 33 months cortisol secretion returned to normal range in all patients; an improvement of metabolic condition was observed in 60, 25, and 50 per cent of hypertensive, diabetic and obese patients respectively.*
CONCLUSION: *Indications to LA in case of AI and SCS is strongly supported by the presence of an associated metabolic syndrome. In spite of a limited number, our experience confirms the favourable results of surgery in such patients.*

KEY WORDS: Adrenal incidentaloma, Laparoscopic adrenalectomies, Subclinical Cushing syndrome

Introduction

Laparoscopic Adrenalectomy (LA) is the procedure of choice for functioning adenomas and the majority of primitive and metastatic malignant lesions [1-4]; few contraindications are represented by neoplastic invasions of adjacent organs and size over 12-15 cm [5-7]. LA has actually replaced open adrenalectomy in most surgical procedures thanks to its lower postoperative morbidity and shorter length of stay [4,8].

LA moreover can be considered the best surgical option for adrenal masses casually discovered during diagnostic imaging performed for reasons unrelated to adrenal disease: the so called incidentaloma (AI) [9-10]. Once an AI has been detected however some steps have to be followed in order to evaluate both its potential malignancy and the occurrence of a subclinical hypercortisolism [11,12]. Such condition is commonly referred to as subclinical Cushing's syndrome (SCS) where typical signs and symptoms of the overt disease are absent. The inap-

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parent secretion of endogenous cortisol instead, may be responsible of metabolic disturbances with the clinical findings of Arterial Hypertension, type 2 Diabetes Mellitus (DM) and Obesity; such conditions are considered factors of increased cardiovascular risk [13-16].
Aim of the present work is to present our experience with LA in a series of adrenal masses operated on for different pathologies that included overt clinical manifestations of hypercortisolism and hyperaldosteronism as well as a series of AI with and without SCS. Our intention is to analyze if surgery can ameliorate the clinical conditions of the metabolic syndrome usually linked with SCS.

Materials and Methods

Our study is based upon retrospective evaluation of medical records of 26 patients submitted to LA at the Department of Endocrine and General Surgery of the University of Cagliari from January 2009 to January 2015. The whole series has been analyzed according to the following items: sex, age, laterality and size of the lesion, indications to surgery (Table I).
Evaluation of LA included operative time, conversion to open surgery, hospital stay, complications and final pathological results (Table II).

TABLE I - *Clinical-pathological data in 26 cases of Laparoscopic Adrenalectomy (LA)*

	N	%
Gender		
Male	5	19
Female	21	81
Age Mean 53.5 (RANGE 30-74)		
30-45	9	34.5
46-60	8	31
61-74	9	34.5
Site		
Left	18	69
Right	8	31
Size (mm)		
<4	16	61,5
4-6	7	27.0
>6	3	11.5
Indications to surgery		
Incidentaloma	11	42.3
Cushing	7	27.0
Suspected metastases	5	19.2
Conn	3	11.5

TABLE II - *Results of surgery in 26 cases of LA*

Average surgical time	162 Minutes (Range 65-225)	
Right	147	
Left	170	
Laparotomic Conversions	4/26	15%
Years		
2009-2011	3/14	21%
2012-2015	1/12	8%
Postoperative Hospital Stay	5.6 Days (Range 3-14)	
Postoperative Complications	3/26	11%
	1 Subcutaneous Emphysema,	
	1 Pleural Effusion,	
	1 Atrial Fibrillation, Hemolitic Crisis	
Pathologic Diagnosis		
Adenoma	20	
Nodular Hyperplasia	2	
Cysts	2	
Myelolipoma	1	
Metastases	1	

The main study was performed in the patients diagnosed as harbouring an AI who also presented one or more items of a metabolic syndrome linked with SCS. Diagnosis of SCS was made in case of failure of cortisol to be suppressed after a nocturnal dose of Desametazone 1 mg (Low Dose Desametazone Suppression Test, LDDST), considering a positive test for values ≥1.8 mcg/dl. Patients were also studied for alterations of serum ACTH, serum cortisol and Urinary Free Cortisol (UFC) (Table III). Blood samples were examined through routine laboratory techniques The same patients were also evaluated for the presence of Arterial Hypertension, Type 2 DM and Obesity.
Arterial Hypertension was defined in cases of sistolic blood pressure ≥ 135 mm Hg and or diastolic blood pressure ≥ 85 or in case of treatment with anthypertensive drugs [13,16] , DM was diagnosed with glucose level higher than 126 mg/dl or in case of treatment with hypoglycemic treatment [13,14,16]. Obesity was considered when BMI was greater than 30 Kg/m^2, while values between 27 and 30 were considered overweight [14].
Results of surgery were evaluated in the short and middle term postoperative periods in order to analyse evolution of clinical conditions and cortical adrenal function. Follow up was scheduled at 6 and 12 months after operation and every following year. Clinical examination was based upon evaluation of arterial pressure, antihypertensive therapy, and Body Mass Index (BMI); while laboratory controls included basal levels of serum ACTH, serum cortisol, UFC and fasting glucose levels. The items were compared with preoperative records. Mean length of follow up was 33 months , ranging from 44 to 13 months (Table IV).

TABLE III - *Clinical and laboratory data in 6 cases of SCS*

Case	Sex	Age	Size /location	Low serum ACTH	High serum cortisol	High UFC	LDDST mcg/dL	Arterial Hypertens	Type 2 DM	BMI
1	F	71	35 left	no	+	+	2.4	+	no	32.7
2	F	59	30 right	no	+	+	2.6	no	no	28.2
3	F	74	61 left	+	no	+	9.2	+	+	38.7
4	M	73	50 right	no	no	+	6.1	+	+	27.5
5	M	70	45 right	+	no	no	6.8	+	+	30.5
6	M	55	35 left	no	no	+	2.3	+	+	36.5

TABLE IV - *Results of surgery and follow up in 6 cases of SCS*

Case	Final diagnosis	Oral cortisone at discharge	Follow up months	High Serum ACTH	High Serum cortisol	High UFC	Improved Arterial Hypertens	Improved DM	Lower BMI
1	Nodular hyperplasia	+	48	no	no	no	+	-	steady
2	Adenoma	+	45	no	no	no	-	-	steady
3	Adenoma	+	41	+	no	no	steady	steady	+
4	Adenoma	no	36	+	no	no	steady	steady	steady
5	Adenoma	+	19	no	no	no	+	steady	+
6	Adenoma	no	13	no	no	no	+	+	+

Results

The whole series of 26 patients is made up of 5 males and 21 females whose mean age was 53.5 (range 30-74). The majority of patients had a left adrenal lesion (18 cases); size of the mass ranged from 21 to 66 mm. Indications to surgery were overt Cushing Syndrome (7 cases), Conn disease (3 cases) incidentalomas (11 cases) and suspected malignant lesion (5 cases) of which only one was confirmed on final pathology (Table I).

LA was always performed through a lateral transperitoneal approach. Results of surgery are reported in Table II: average lenght of LA was 162 minutes (range 65-225) slightly shorter for the right lesions (147 min) compared to the left ones (170). Four patients were converted to open surgery (15%); reasons to conversion were: bleeding (2 cases), difficult access to the adrenal vein, and fragmentation of the adrenal gland. Rate of conversion has changed during the years time, passing from 21 to 8% if the first and second half of the series is concerned (Table II)

No mortality was observed. Complications occurred in three cases: subcutaneous emphysema, pleural effusion, while a third patient underwent atrial fibrillation and hemolitic crisis due to G6PD deficiency. All these complications were treated conservatively.

Mean hospital stay was 5.6 days ranging from 3 to 14 days. Histopathology on the surgical specimen proved 20 adenomas, 2 nodular hyperplasia, 2 cysts, 1 myelolipoma and 1 adrenal metastases of a thyroid carcinoma.

As far as the 11 AI are concerned, a diagnosis of SCS was made in 6 cases and they are the object of our main analysis. As already mentioned a SCS was recognized according to a positive LDDST and concomitant several alterations of ACTH/cortisol secretion. The patients were 3 males and 3 females with a mean age of 67.8 years; AI were equally distributed in the right and left location; mean size was 42.6 mm (range 30-61)

In addition to a positive LDDST, five patients had also increased levels of UFC, two patient decreased ACTH levels and two patients elevated morning values of serum cortisol (Table III).

Together with laboratory alterations of ACTH/cortisol secretion, variable patterns of metabolic syndrome were detected: Arterial Hypertension was present in 5 cases; DM in 4 cases, Obesity and overweight in 4 and 2 cases respectively. The 3 conditions were simultaneously associated in 3 patients. All cases with hypertension and DM were under therapy (Table III)

Results of surgery and follow up of the 6 cases are reported in Table IV: a single case required conversion to open surgery. Pathology on the surgical specimen showed 5 cortical adenomas and 1 nodular hyperplasia. Four patients required cortisone acetate administration due to temporary inhibition of contralateral gland at the time of discharge. Oral cortisone was discontinued after a few weeks time, except a single case that required nearly 20 months of prolonged treatment for failure of the resting gland ; the same patient had high levels of serum ACTH. All the patients are alive and apparently in good clini-

cal conditions at the time of the follow-up. In all of them was observed a return to normal values of serum cortisol and UFC while high levels of serum ACTH were recognized in two patients: in one case due to failure of the resting gland and in the other due to autonomous secretion.
In the 3 cases of the 5 with arterial hypertension a better control of mean arterial pressure was achieved that brought to a reduction of therapy ; only one case among the 4 with DM gained improvement of the disease through better control of glycemic levels and interruption of a single drug. A decreased BMI was observed in 3 cases with values not much lower than the preoperative levels; in 3 cases BMI remained steady (Table IV).

Discussion

The present work is based upon the experience resulting from a series of 26 LA performed in the time span of 6 years. LA has been started in our Institution in January 2009, when technical expertise was gained following several training courses in advanced laparoscopy in tertiary referral Centres by some of the Authors. In the years before and during the same year, other 5 open adrenalectomies had been performed, but since 2009 all procedures on adrenal glands underwent a laparoscopic approach.
Indications to surgery in the 26 cases included overt clinical Cushing Syndromes and Conn diseases even if the majority of patients were operated on because of an AI (11 cases) and for adrenal masses in suspicion of malignancy (5 cases). In the same series a single case of vascular anomaly with a duplicated Inferior Vena cava has been object of a case report [17].
Considering surgical results our series presents an operative time and a conversion rate which are slightly over the values commonly reported [8,18]: we believe this is due to a learning curve that is actually reaching a standard level, so that in the second half of our experience, conversion rate (8%) is comparable with the results of leading Centers in LA [1,3,7,19-22].
The absence of mortality and the low complications rate confirm our good enough results.
It is worth to note that in spite of the suspicion of primitive or metastatic involvement for 5 adrenal masses, final pathology proved that adrenal metastases was eventually detected in a single case. Such finding is in order on what commonly reported: overall incidence of adrenal primitive or recurrent malignancy in unselected series ranges from 1 up to 15% [3,6,22-24].
Neither a primary malignant lesion nor a recurrence however is a contraindication to surgery unless invasion of adjacent organ requires enlarged excision [6].
All cases of our series were operated on through a transperitoneal lateral technique which is actually the approach most frequently adopted in LA [5,8,18,23-26]. According to a review by Assalia and Gagner, transperitoneal lateral approach is adopted nearly in 80 % of LA [8]. We have no experience in the anterior and retroperitoneal posterior approach proposed by other Authors [2,7,22].
Addressing now to the main issue of the present work, that is AI, this is commonly defined as an adrenal mass casually discovered after imaging diagnostic procedures performed for reasons other than adrenal disease [11,16]. AI is not a simple matter to get on: some Authors observe that AI rather than a single entity is an umbrella definition comprising different pathological entities [12].
It is well known that incidence of AI has become a common finding with the widespread use of high definition imaging techniques [12,13,27-30]. Incidence of AI in autoptic studies ranges from less than 1% for patients younger than 30 years, up to 7% in patients 70 years of age or older [28]; the same data are reported in radiological studies with a frequency estimated around 4% in middle age and increases up to 10% in the elderly [12].
Initial appraisal of AI is truly based upon accurate evaluation of the imaging phenotype (mainly CT and MRI) with the aim to determine its potential malignancy : major criteria in favour of malignant disease are a lesion larger than 4 cm, irregular in shape with mixed densities, usually vascular, > 25 Hounsfield units and a wash out of contrast after 15 min less than 40% [11,30]. Malignancy is an uncommon cause of incidentaloma in patients not known to have cancer [30]. In a series of 2005 patients with AI, incidence of adrenocortical carcinoma and metastatic cancer were 4.7 and 2.5 % respectively [11]. Size is certainly important in such evaluation: adrenal cortical carcinoma accounts for 2% of lesions that are 4 cm or less, 6% of tumors that are 4.1 to 6 cm and 25% of tumours that are greater than 6 cm [28].
As far as size is concerned, in the present series lesions larger than 4 cm were observed in three cases, but no other sign of suspicion was detectable, in particular no mixed density nor increased HU [27]; size was however one of the items for referral to surgery. In our experience a preoperative diagnosis of a benign disease was confirmed by final pathology on the surgical specimen which proved 5 cortical adenomas and 1 multinodular hyperplasia.
The second point to be appraised in case of AI relates to its functional status. The majority of AI are non functioning adenomas; viceversa a secreting AI in the great majority of cases is associated with a subtle production of cortisol [12]; functioning AI with inapparent increased secretion of cathecolamines and aldosterone can not be exclude but have been less frequently reported [11,12,16].
Occurrence of autonomous cortisol production in AI is detected with ranges from 5 to 30 % but its average can be estimated around 20% [12-14,16,28,29,31].
In our experience increased cortisol secretion was observed in 54.2 % of the 11 AI, a value which is certainly higher than what commonly reported: this can be explained by the small number of our patients and by

the cut off limit of 1.8 mcg/dl that we chose for defining a positive LDDST. Obviously a lower limit increases the percentage of SCS that can be detected but at the expenses of a lower specificity [11,12]. For this reason some Authors advocate a cut off value of 5 mcg/dl [11,28,30], others of 3 mcg/dl [13,29], in favour of an increased specificity. Others again keep a value of 1.8 together with at least one of the following items: morning ACTH < 10 pg/ml, UFC > 100 and altered diurnal cortisol circadian rhytm [16]. In effect this has been also our policy because LDDST was not the only item we selected for establishing the occurrence of a SCS: as already mentioned five patients had increased levels of UFC, two of them had high levels of serum cortisol and two others low morning ACTH levels.

Recognition of a SCS can be difficult in cases where the inapparent cortisol secretion looses its usual diurnal circadian cycle so that blood samples taken in routine circumstances may not demonstrate the increased levels; unfortunately other recently proposed methods such as late night salivary cortisol can not rule out SCS in patients with AI [12,30].

For this reason in patients harbouring an AI coupled with a borderline SCS we believe very important the evaluation of an associated metabolic syndrome. We know that such findings are not always present and in the same time most of the manifestations of hypercortisolism, ie hypertension, obesity and diabetes are not specific and are commonly observed in the general population [13].

Other authors, with the same purpose, have also considered the presence of an altered lipidic profile and of osteoporosis for a further evaluation of a metabolic syndrome [13,14]; such items were not studied in our present work but they can be considered a further support to justify a surgical approach.

It is important to note that the mean age of the 6 cases discovered with AI and SCS was of 66 years while in the whole series the mean age of patients with overt Cushing syndrome was of 44 years. Such finding, already noticed by others, could be explained by the longer time required to develop symptoms in case of relatively low cortisol levels compared with classical Cushing syndrome [13].

Based on these premises, what criteria should guide the decision on surgical versus non operative treatment of an AI after its evaluation in imaging phenotype, functional status and concurrent metabolic syndrome? The answer to this question is not univocal. The risks of surgery have to be balanced with a less invasive medical therapy, provided it can effectively control the consequence of the metabolic syndrome In older patients with adrenal masses ≤ 3 cm with sublinical hypercortisolism a waiting policy has been advocated with a periodical laboratory and instrumental control [30].

Erbil et al observe that patients with inapparent hypercortisolism should still be considered at atherogenic risk –independent from SCS and long term follow up should be implemented as well as prevention of cardiovascular risk factors [13].

For this reason several studies have been performed comparing the results of surgery and medical treatment in cohorts of patients with AI and SCS: the majority of these studies are based on retrospective evaluation , but all of them report more favourable results of surgical treatment versus the medical one [9,12,15,16,31]. In a single prospective randomized study the patients undergone to surgery had a normalized or improved conditions of hypertension, DM and obesity whereas a worsening of same items was observed in the conservatively managed patients [32].

A very recent systematic metanalysis by Iacobone et al on the surgical treatment of SCS was made on a screening of 105 papers: of them seven were selected for satisfactory requisites but among them only one was a randomized study: the results are related to 230 patients and show that surgery ameliorates hypertension, DM and obesity in 72, 46 and 39 % of the patients respectively [33].

In the present series, recognition of a SCS associated to an AI was made in 6 cases among 11, both for the hormonal pattern and for variable aspects of a metabolic syndrome. Not every patient had synchronous association of arterial hypertension, DM and obesity, but at least two of these clinical conditions were present in all of them.

In our experience referral to surgery (ie to LA) was then supported by an incidentally discovered adrenal mass, not negligible in size (average 42 mm), associated to an altered cortisol secretion and moreover with simultaneous occurrence of metabolic disturbances.

Results of LA have already been reported on the overall series that includes also the six cases of SCS. As far as the hormonal status is concerned all patients returned to normal cortisol levels during the follow up. This is confirmed also by the postoperative requirement of oral cortisone administration in 4 patients due to the partial inhibition of the remaining adrenal gland. Metabolic outcomes were good enough but not very brilliant : patients with arterial hypertension had a proportional major benefit from surgery than patients with diabetes and obesity did.

Conclusion

Indications to LA in case of AI should be stated according to several items that include diagnostic imaging techniques, clinical findings and study of cortisol-ACTH secretion.

In case of AI linked with a suspected SCS, a positive LDDST is the mainstay towards a surgical decision. The further presence of the signs of a metabolic syndrome makes surgical decision stronger even in the cases were LDDST results are borderline. According to our personal

experience and review of Literature most of the patients with AI and SCS have benefit from surgery specially considering the short recovery and less painful postoperative course linked with LA.

Riassunto

Il riscontro di un incidentaloma surrenalico comporta un approfondimento diagnostico rivolto da un lato a chiarire la natura della lesione e nello stesso tempo ad accertare la presenza di una attività endocrina subclinica. Quest'ultima molto spesso è caratterizzata da una sindrome metabolica nella quale sono presenti Ipertensione arteriosa, Diabete Mellito di tipo 2 ed Obesità. Tali manifestazioni cliniche, indotte da una alterata secrezione cortisolica, configurano quindi una Sindrome di Cushing subclinica (SCS) nella quale, con il passare del tempo può verificarsi una compromissione della funzione cardiaca nonché un aggravamento del DM e dell'obesità. L'attuale orientamento di fronte ad una SCS, pur oggetto di dibattito, è a favore della surrenectomia laparoscopica (SL), anche in rapporto ai favorevoli risultati della terapia chirurgica nei confronti del trattamento medico.

Gli Autori alla luce dell'esperienza personale su 26 casi di SL effettuati in un periodo di 6 anni, riportano i loro risultati in merito alla casistica generale e in particolare nei casi in cui era riconoscibile una SCS. Scopo del lavoro: verificare nel tempo se la SL ha comportato una normalizzazione dell'alterata secrezione cortisolica e un miglioramento della sindrome metabolica associata.

Nell'arco temporale gennaio 2009-gennaio 2015 presso il Reparto di Chirurgia Generale A del Policlinico Universitario di Monserrato sono state effettuate 26 SL in 5 maschi e 21 femmine di età media di 53 anni. Le indicazioni alla SL comprendevano 11 incidentalomi, 7 sindromi di Cushing, 5 lesioni sospette per metastasi e 3 sindromi di Conn. Le SL sono state portate a termine in 22 casi (percentuale di conversione 15%), la durata media dell'intervento è stata di 162 minuti (range 65-225) Nessuna mortalità e complicanze pari all'11%. Degenza media postoperatoria 5,6 giorni. L'esame istologico definitivo ha evidenziato 20 adenomi corticali, 2 iperplasie nodulari, 2 cisti, 1 mielolipoma, 1 metastasi di carcinoma.

Sei casi degli 11 incidentalomi presentavano una SCS diagnosticata attraverso la determinazione del test di soppressione con Desametazone a basse dosi; il test è stato considerato positivo per valori ≥ 1.8 mcg/dL. Negli stessi pazienti erano presenti alterazioni della secrezione ACTH/cortisolo e forme diverse di una sindrome metabolica: 5 casi presentavano ipertensione arteriosa, 4 DM, 4 BMI > 30; 3 pazienti avevano associate le tre forme cliniche. I dosaggi del cortisolo e dell'ACTH serico, l'Ipertensione arteriosa, il DM e l'indice di massa corporea sono stati controllati a distanza e confrontati con i valori pre-operatori. Il follow up è risultato in media di 33 mesi.

Nel controllo a distanza tutti i pazienti erano in buone condizioni cliniche; i valori del cortisolo ematico e del cortisolo libero urinario si sono normalizzati in tutti i pazienti, mentre due di essi presentavano valori dell'ACTH più alti della norma. In 3 casi su 5 di ipertensione arteriosa si è osservato una riduzione di valori pressori e un miglior controllo farmacologico. Un caso su 4 di DM ha avuto un miglioramento del controllo glicemico. In 3 casi su 6 il BMI si è ridotto anche se con valori non significativi.

Nell'esperienza personale i pazienti affetti da SCS associata all'incidentaloma hanno avuto una normalizzazione del quadro ormonale e mediamente un miglioramento della sindrome metabolica.

Quest'ultima rappresenta quindi un' ulteriore indicazione alla chirurgia anche nella prospettiva della riduzione del rischio cardiovascolare. La SL è la procedura di scelta in rapporto alla minore entità del trauma e ai precoci tempi di recupero.

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