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Case Series and Review of Literature

The Incidence of Long-Term Adrenal Insufficiency Following Unilateral Adrenalectomy is Low: Case Series and Review of Literature

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ABSTRACT

Introduction: Acquired adrenal insufficiency is a known risk of unilateral adrenalectomy. However, the rates of early and prolonged adrenal insufficiency following unilateral adrenalectomy are not well defined in the literature.

Patients and Methods: We reviewed a case series of 184 consecutive patients to determine the likelihood of steroid supplementation at 30 days and 1 year following adrenalectomy. 109 lesions were non-functional and 75 (41%) demonstrated functionality, including 33 pheochromocytomas, 20 cortisol-producing adenomas, 19 aldosteronomas, and 3 cases of cortisol-secreting hyperplasia. No patients with a non-functional lesion, pheochromocytoma, or aldosteronoma required steroid supplementation following surgery. Eleven of 23 patients (48%) with primary adrenal Cushing syndrome required cortisol supplementation at 30 days, and only 1 patient (4%) necessitated supplementation one year following surgery.

Discussion: Approximately 50% of patients with cortisol-producing lesions in the adrenal gland will require supplementation 30-days following surgery. Only 4% will require persistent exogenous steroids at 1-year. Conversely, less than 1% of patients with different types of functional or non-functional tumors required supplementation after surgery.

Conclusion: The incidence of adrenal insufficiency following unilateral adrenalectomy is low. A large majority of patients requiring steroid supplementation 30 days following surgery are able to wean off this requirement by 1 year. With this information, we can better counsel our patients and set clearer expectations for the potential need of cortisol supplementation following adrenalectomy.

Introduction

Adrenalectomy by an open or minimally invasive approach is performed to treat a variety of functional and non-functional tumor pathologies [1]. Depending on tumor type, some patients with functional adrenal adenomas or hyperplasia will experience suppression of their hypothalamic-pituitary-adrenal hormonal axis [2]. This is particularly true for cortisol secreting adrenal tumors, which render a functional hyper cortisol state and therefore primary adrenal Cushing syndrome [3]. Following unilateral removal of an overactive adrenal gland, the contralateral gland may be unable to compensate initially until the pathway recalibrates following prolonged suppression [4]. Appropriate exogenous supplementation is therefore necessary over this time to minimize the risk of acquired adrenal insufficiency, which may manifest as fatigue, hypoglycemia, hypotension, and dehydration [5].

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The rates of early and prolonged adrenal insufficiency following unilateral adrenalectomy are incompletely defined in the literature [6-8]. Indeed, knowledge of this is essential for appropriate patient counseling and expectations for therapy needed after surgery. Therefore, the purpose of our investigation was to determine the practical implications of adrenal insufficiency following unilateral adrenalectomy. To do so, we conducted a case series along with a review of the literature to determine the incidence of adrenal insufficiency in patients undergoing adrenalectomy for all indications and to describe how frequently cortisol supplementation is required at 30 days and 1 year postoperatively.

Patients and Methods

Adrenalectomies performed between December 2004 and June 2016 at a single tertiary care academic medical center were retrospectively reviewed following IRB approval. Cases were identified by querying billing data based on CPT codes. Cases were included for all twelve surgeons who performed these operations and for male and female patients aged 18 and older. Exclusion criteria included concurrent resections of organs other than the adrenal gland or concurrent surgical procedures (such as nephrectomy) as well as lack of patient data available in the electronic medical record. We recorded patient characteristics, surgical parameters, and tumor pathology to evaluate for any risk factors that may predict extended cortisol requirements. Charts were reviewed to determine which patients required steroid replacement at 30 days and at 1 year following surgery. Logistic regression was used to determine if any patient risk factors cousld predict need for exogenous steroids at 30 days. Significance was set at 0.05.

Table 1: Clinical characteristics of unilateral adrenalectomy cohort.

Total patients	184	
Age (mean, range)	54	19 - 82
Gender (#, %)		
Male	70	38%
Female	114	62%
Surgical Approach (#, %)		
MIS	167	91%
Open	17	9%
Side (#, %)		
Left	110	60%
Right	74	40%
Pathology (#, %)		
Benign	161	88%
Malignant	23	12%
Functionality (#, %)		
Functional	75	41%
Non-functional	109	59%
Lesion size (cm) (mean, range)	3.7	1.2 - 11.1
Estimated blood loss (mL) (mean, range	75	25 – 900
OR duration (min) (mean, range)	168	63 - 285

Results

The salient clinical characteristics of the unilateral adrenalectomy cohort are highlighted in (Table 1). Briefly, 184 total unilateral adrenalectomies were performed including 167 (91%) by a minimally invasive approach. Pathologic characteristics noted a mean tumor size of 3.7cm, 161 (88%) lesions were benign, and 75 (41%) were functionally active. Table 2 highlights the pathologic characteristics of the resected adrenal masses. Of the 184 adrenal lesions, 75 (41%) demonstrated functionality including 33 pheochromocytomas, 20 cortisol-producing adenomas, 19 aldosteronomas, and 3 cases of cortisol-secreting hyperplasia. 109 (59%) of the lesions were non-functional and 23 were malignancy (either primary adrenal or metastatic from a different primary).

Of the patients with functional adrenal tumors, no patients with either a pheochromocytoma or an aldosteronoma required supplementation with exogenous steroids following the surgical adrenalectomy. Eleven of 23 patients (48%) with primary adrenal Cushing syndrome required cortisol supplementation at 30 days, and only 1 patient (4%) necessitated supplementation one year following surgery (Figure 1). When considering the entire unilateral adrenalectomy cohort, 6% of had adrenal insufficiency at 30 days and 0.5% at one year with all of these patients having cortisol secreting lesions. Patient characteristics evaluated as potential predictors of risk for prolonger cortisol supplementation included age, gender, body mass index, smoking status, American Society of Anesthesiologists score, diagnoses of diabetes, hypertension, congestive heart failure, or chronic obstructive pulmonary disease, and pathologic diagnosis of adrenal malignancy. Interestingly, female gender (61% of this cohort) was the only significant risk factor associated with adrenal insufficiency at 30 days (10% of females vs. 0% of males, $p<0.01$).

Table 2: Pathologic Characteristics of Resected Adrenal Masses.

Pathologic Diagnosis	**Frequency**	**Percentage**
Functional Tumors	**75**	**41%**
Pheochromocytoma	33	18%
Adrenal adenoma, cortisol-producing	20	11%
Adrenal adenoma, aldosterone-producing	19	10%
Adrenal cortical hyperplasia, cortisol-producing	3	2%
Non-Functional Tumors	**109**	**59%**
Adrenal adenoma, nonfunctional	38	21%
Adrenal cortical hyperplasia	19	10%
Metastasis, other than renal cell carcinoma	13	7%
Benign cyst	10	5%
Myelolipoma	8	4%
Metastasis, renal cell carcinoma	6	3%
Ganglioneuroma	5	3%
Pseudocyst	5	3%
Adrenal cortical carcinoma	4	2%
Hematoma	1	1%
Total	**184**	**100%**

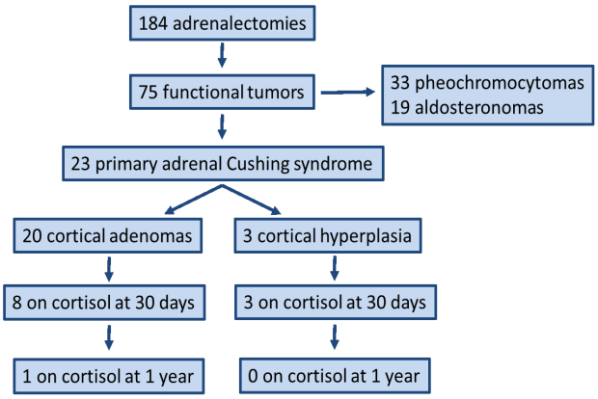

Figure 1: Adrenal Insufficiency by Tumor Pathology Following Unilateral Adrenalectomy.

Discussion

In this case series study, we identified that approximately 50% of patients with cortisol producing lesions in the adrenal gland will require supplementation 30-days following surgery and only 4% will require persistent exogenous steroids at 1-year. Conversely, no other patients with different types of functional or non-functional tumors required supplementation after surgery. For these patients, at 1-year following adrenalectomy, only 0.5% was on exogenous steroids. Interestingly, female gender was associated with need for supplementation in the cortisol secreting population although a biologic explanation for this gender association is frankly unclear and may simply be a function of sample size. Standard evaluation for a patient with an adrenal tumor entails a metabolic evaluation to diagnose functional tumors [9, 10]. At our institution and others, all patients with evidence of hypercortisolism are placed on glucocorticoid supplementation following surgery to prevent adrenal crisis. This supplementation is weaned post-operatively, although recovery of endogenous cortisol production is sometimes prolonged [6].

A review of the literature shows that cortisol supplementation is typically needed following adrenalectomy for Cushing syndrome, and not necessarily for adrenalectomies for other indications [7]. When an adrenal gland is removed for non-Cushing pathology such as an aldosteronoma, ACTH levels appropriately increase in a short interval to ensure stabile secretion of cortisol by the contralateral gland [8]. Our findings are concordant with these findings. Berr and colleagues investigated this by comparing time to adrenal recovery following curative surgery for Cushing Disease, adrenal Cushing syndrome, and ectopic Cushing syndrome [11]. These authors found that the underlying etiology was predictive of adrenal recovery, with adrenal Cushing syndrome patients weaning off hydrocortisone at a median of 2.5 years. The duration of steroid supplementation for primary adrenal Cushing syndrome has also been studied by Prete and colleagues who noted that nearly 90% of patients continued to require hydrocortisone 2 months after surgery, with a median duration of adrenal insufficiency of 6 months and 18.5 months for those with subclinical and overt Cushing syndrome, respectively [12]. One limitation of our work is variability of follow-up interval. As patient follow-up was not standardized, 30-day and 1-year cutoffs were used to broadly characterize supplementation needs. Furthermore, the degree and severity of clinical or subclinical hypercortisolism for patients was not fully characterized. Prior work has suggested that the time to recovery of adrenal function is related to the degree of hypercortisolism prior to surgery [13]. Finally, the sample size of 23 patients with primary adrenal Cushing Syndrome is relatively low, perhaps limiting ability to demonstrate significance of risk factors examined. In light of these limitations, the current series has identified and filled a gap in the literature, although further study and data is warranted.

Nonetheless, we noted that approximately half of patients with cortisol secreting tumors were able to taper off of steroid supplementation over the first month, with only 1 patient in this data series demonstrating evidence of persistent adrenal insufficiency at 1-year. We believe these data suggest that recovery of adrenal function following adrenalectomy for Cushing Syndrome may occur sooner than previously described. Further investigation is needed to elucidate why some individuals require an extended course of glucocorticoids. For patients with non-cortisol secreting tumors, none required cortisol supplementation post-surgery thereby confirming observations from prior investigations. These data may further help physicians counsel patients regarding expected postoperative course for cortisol supplementation following adrenalectomy.

Conclusion

The incidence of adrenal insufficiency following unilateral adrenalectomy is low. Most patients who need steroid supplementation 30 days following surgery are able to wean off this requirement by 1 year.

Conflicts of Interest

No conflicts of interest to disclose.

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