Endocrinology, Diabetes & Metabolism CASE REPORTS

K Grønning and others | Adrenal insufficiency due to lymphoma

ID: 19-0131; March 2020
DOI: 10.1530/EDM-19-0131

Primary adrenal lymphoma as a cause of adrenal insufficiency, a report of two cases

Kaja Grønning[1], Archana Sharma[1], Maria Adele Mastroianni[2], Bo Daniel Karlsson[3], Eystein S Husebye[4,5], Kristian Løvås[4,5] and **Ingrid Nermoen[1,6]**

[1]Department of Endocrinology, Akershus University Hospital, Lorenskog, Norway, [2]Department of Haematology, Akershus University Hospital, Lorenskog, Norway, [3]Department of Radiology, Akershus University Hospital, Lorenskog, Norway, [4]Department of Clinical Science and K.G. Jebsen Center of Autoimmune Disorders, University of Bergen, Bergen, Norway, [5]Department of Medicine, Haukeland University Hospital, Bergen, Norway, and [6]Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway

Correspondence should be addressed to K Grønning
Email
kaja.gronning@gmail.com

Summary

Primary adrenal lymphoma (PAL) is a rare cause of adrenal insufficiency. More than 90% is of B-cell origin. The condition is bilateral in up to 75% of cases, with adrenal insufficiency in two of three patients. We report two cases of adrenal insufficiency presenting at the age of 70 and 79 years, respectively. Both patients had negative 21-hydroxylase antibodies with bilateral adrenal lesions on CT. Biopsy showed B-cell lymphoma. One of the patients experienced intermittent disease regression on replacement dosage of glucocorticoids.

Learning points:

- Primary adrenal lymphoma (PAL) is a rare cause of adrenal insufficiency.
- Bilateral adrenal masses of unknown origin or in individuals with suspected extra-adrenal malignancy should be biopsied quickly when pheochromocytoma is excluded biochemically.
- Steroid treatment before biopsy may affect diagnosis.
- Adrenal insufficiency with negative 21-hydroxylase antibodies should be evaluated radiologically.

Background

Primary adrenal insufficiency is characterized by low or subnormal serum cortisol and elevated levels of adrenocorticotropic hormone (ACTH). Patients also have low aldosterone and elevated plasma renin. Elevated ACTH and low aldosterone distinguish primary adrenal insufficiency from secondary adrenal insufficiency, where cortisol is low with low ACTH and normal aldosterone. Other biochemical disturbances in primary adrenal insufficiency are hyponatremia (84–88%), hyperkalemia (36–64%) and elevated TSH (50%) (1). Clinically, fatigue and weight loss is reported in 100%, anorexia and nausea/vomiting in 80–90%, hyperpigmentation in >90% and low blood pressure in 90% (2). ACTH stimulation test confirms the diagnosis. The condition may progress to adrenal crisis and death. Causes of adrenal insufficiency include autoimmune adrenalitis, infections, infiltrative disorders and malignancy. We hereby report two patients presenting with adrenal insufficiency with negative 21-hydroxylase antibodies and bilateral adrenal lesions.

Case presentations

Case report 1

A 70-year-old man with former mechanical ileus and gout experienced 12 kg weight loss, nausea, anorexia, orthostatic dizziness and joint pain. Because of an elevated creatinine at 250 µmol/L, he was admitted for evaluation of kidney failure.

ID: 19-0131; March 2020
DOI: 10.1530/EDM-19-0131

Investigations

Blood pressure was 96/70 mmHg, serum sodium: 133 mmol/L (137–145 mmol/L) and serum potassium: 6.2 mmol/L (3.5–5.0 mmol/L). On clinical suspicion, a paired morning cortisol and ACTH was taken, revealing cortisol at 98 nmol/L (112–502 nmol/L) and ACTH at 164 pmol/L (1.4–14 pmol/L). A synacthen test (250 µg i.v.) showed no increase in cortisol. Replacement treatment was commenced with excellent effect. 21-hydroxylase autoantibodies were negative, and contrast-enhanced CT revealed bilateral adrenal masses, a 4.3 x 2.5 cm lesion on the right side and a 2.1 x 1.8 cm lesion on the left side. A subsequent biopsy showed diffuse large B-cell lymphoma.

Treatment and follow-up

He received six treatments with cyclophosphamide, vincristine, doxorubicine and prednisolone (CHOP) followed by radiation therapy. Replacement therapy with cortisone acetate 25 mg twice daily and fludrocortisone 0.15 mg was started. Nine years after treatment, he was diagnosed with CNS lymphoma and died about 5 months later.

Case report 2

A 79-year-old man with prior testicular and bladder cancer, deep venous thrombosis and mild hypothyroidism presented with acute kidney failure. Prior to admission, he had 1 month history of weight loss, fatigue and nausea/vomiting. At presentation, his regular medication consisted of thyroxine replacement therapy, tamsulosin and low-molecular weight heparin (the latter instead of oral anticoagulation due to bleeding tendency).

Investigations

Biochemistry showed acute kidney failure (creatinine 265 µmol/L) and hyponatremia (131 mmol/L). During the next 3 days, plasma sodium decreased to 120 mmol/L despite treatment with i.v. isotonic sodium chloride. Urinary sodium was 26 at presentation, increasing to 68 during treatment. Urine osmolality was 392 mosm/kg measured at the same time as the second urinary sodium. The first urine sodium could be explained by hypovolemia. Increasing urinary sodium content with falling plasma sodium raised suspicion of SIADH. Further assessment revealed low serum cortisol at 37 nmol/L (112–502 nmol/L) and grossly elevated ACTH at 87.7 pmol/L (1.4–14 pmol/L). Synacthen test (250 µg i.v.) confirmed primary adrenal insufficiency (Table 1). On reconsideration, this explained hyponatremia with high urinary sodium. Because of negative 21-hydroxylase antibodies, a CT scan was undertaken, revealing bilateral adrenal masses (Fig. 1A). The right lesion consisted of two parts: a ventral lesion with diameter 1.8 cm and precontrast density 25 Hounsfield Units (HU) and a dorsal part measuring 1.6 cm with precontrast density 30 HU. Washout was 74% for the ventral lesion and 55% for the dorsal lesion. On the left side, the mass measured 4.2 x 2.1 cm with precontrast density 32 HU and washout 32% (Fig. 1B). High precontrast density and modest washout of the right dorsal lesion and the left mass was suggestive of metastases. There were no other signs of malignancy. Normal plasma metanephrines excluded pheochromocytoma.

Treatment and follow-up

Recovery was rapid after stabilization with i.v. hydrocortisone 100 mg intravenously three times during the first 24 h followed by oral replacement therapy with cortisone acetate 25 mg x 3 with gradual reduction to 25 + 12.5 mg and fludrocortisone 0.1 mg daily. MRI after 4 weeks confirmed bilateral adrenal lesions with characteristics pointing toward malignancy. He was planned for a CT-guided biopsy. Due to the Easter vacation and a mistake concerning the appointment, it took almost 1.5 months from the MRI (2.5 months from first presentation) until biopsy was scheduled. By then, the malignant-looking masses had almost disappeared. The right ventral lesion was unchanged, whereas the right dorsal lesion was undetectable and the left measured 8 mm

Table 1 Baseline laboratory values and synacthen test.

	Patient 1	Patient 2	Reference
S-cortisol, nmol/L			
0	193	37	112–502
30 min	175	46	
60 min	173	40	>500
ACTH, pmol/L			
0	191	87	
30 min	81.6		
60 min	93.1		1.4–14
S-sodium, mmol/L	133	131	137–145
S-potassium, mmol/L	5.5	6.0	3.5–5.0
Aldosterone, pmol/L	<69	97	<653*
Renin, mIU/L	4.8	27.8	2.8–39.9*

*Laying down.

ID: 19-0131; March 2020
DOI: 10.1530/EDM-19-0131

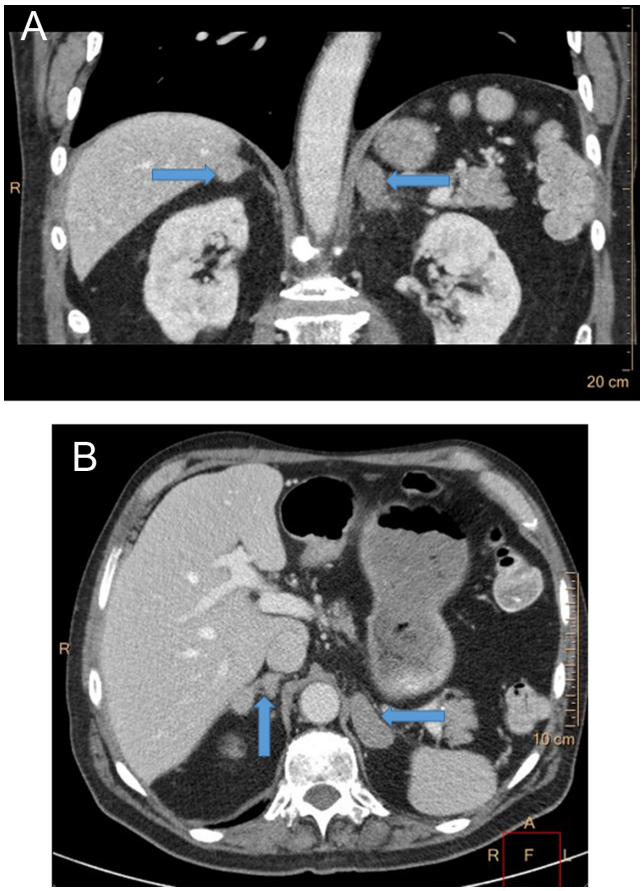

Figure 1
Contrast-enhanced computed tomography (CT) of the adrenals in patient 2 showing bilateral masses (arrows). Right-sided lesion consisting of two parts with ventral diameter measuring 1.8 cm and dorsal diameter measuring 1.6 cm. The left lesion measures 4.2 × 2.1 cm.

(Fig. 2). Biopsy was not performed. On reconsideration, the lesions were thought to represent hemorrhage or infection with spontaneous recovery. The patient was in good condition on replacement therapy with regular follow-up at the endocrinology outpatient clinic.

Six months later he presented acutely with fever, tachycardia and hypotension without focal infection signs. Prior to admission, he had a 3 months history of abdominal discomfort, nausea and 10 kg weight reduction with a positive test for occult fecal bleeding. Gastrointestinal pathology had been excluded by endoscopic examinations. Subsequent abdominal CT had revealed a large mass in relation to the right adrenal. This finding was not yet evaluated. On acute admission, he had progressive systemic inflammatory response syndrome despite therapy with i.v. fluids, hydrocortisone and broad spectrum antibiotics. No infection was identified on urinary analyses and pulmonary X-ray. Abdominal CT confirmed a heterogenous tumor of the

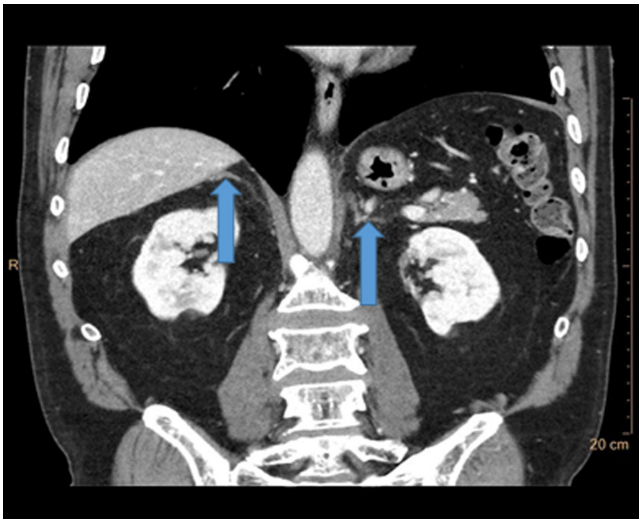

Figure 2
Adrenal CT 2 months later. Almost total regress of the right dorsal lesion and the left lesion. The right ventral lesion is still present (adenoma according to wash-out analyses).

right adrenal measuring 6.0 x 7.0 x 12.0 cm (Fig. 3A), growing into liver parenchyma and infiltering adjacent lymph nodes. The left adrenal was atropic (Fig. 3B). A biopsy was performed, showing aggressive diffuse large B-cell lymphoma with high proliferation index (Ki67 of 100%). Standard treatment with six courses of rituximab, cyclophosphamide, vincristine, doxorubicine and prednisolone (R-CHOP) followed by radiation therapy was initiated. Therapy was successful without signs of tumor recurrence at last follow-up, 2 years after treatment. The patient still takes replacement therapy for adrenal insufficiency and is seen by endocrinologist regularly.

Discussion

Primary adrenal lymphoma (PAL) is uncommon. In a systematic review by Rashidi & Fisher (3), it is defined

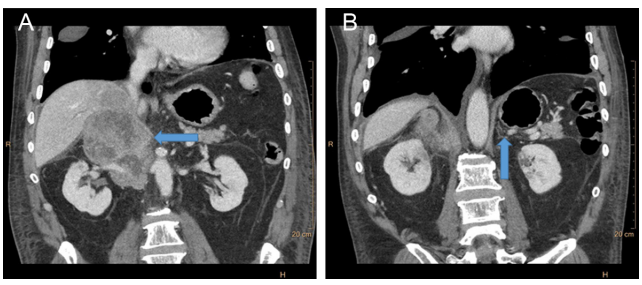

Figure 3
Adrenal CT 7 months after spontaneous regress. Heterogenous tumor of the right adrenal measuring 6 × 7 × 12 cm (A). Atropic left adrenal without mass (B).

ID: 19-0131; March 2020
DOI: 10.1530/EDM-19-0131

as histologically proven lymphoma involving one or both adrenal glands, with no prior history of lymphoma elsewhere and adrenal lesions dominating over lymph nodes or other organs involved. PAL is bilateral in about 70% of cases. Radiologically, the lesions tend to show low density and slight to moderate contrast enhancement on CT. On MRI, the tumors tend to be iso-/hypo-intense in T1 and hyperintense in T2 (3). In Rashidi & Fisher's material, all masses studied with PET and Gallium scans showed increased uptake demonstrating high metabolic activity. Angiographic studies showed low vascularity. A definitive diagnosis is made histologically and requires biopsy. The most common subtypes are diffuse large B-cell lymphoma (DLBCL) accounting for 78% and peripheral T-cell lymphoma (PTCL) – 7%. Tumor behavior is aggressive with B-symptoms in 68% and adrenal insufficiency in 61%. Other manifestations include pain (42%) and fatigue (36%). Only 1% are found incidentally. Demographic studies show male predominance (1,8:1) with mean age 62 ± 14 years. Causes of bilaterality is not fully understood. According to Rashidi & Fisher, 'field effect' with simultaneous cancers of an anatomic 'field' (like an organ or gland) with genetically altered cells is one possible mechanism. Organotropism (affinity of tumour cells for certain tissues) is also suggested. As the adrenal parenchyma lacks lymphatic vessels, lymphomagenesis outside the organs before 'homing' to the adrenals is proposed. Chemokine- and microRNA-driven organotropism in CNS and testicular lymphoma is under investigation, and similar mechanisms could exist in the pathophysiology of primary adrenal lymphoma (3). The authors pinpoint that more research is needed to explain the pathophysiology and bilaterality of primary adrenal lymphoma. B-symptoms are associated with bilaterality, thought to reflect greater systemic cytokine-effects from lymphomas with larger tumour burden and greater access to blood and lymphoid vessels. There was a significant association between bilaterality and adrenal insufficiency. No concrete example of unilaterality and adrenal insufficiency was mentioned. On the other hand, even small primary adrenal lymphomas have been associated with adrenal insufficiency. This observation has led to a suggestion that the correlation between tumor size and adrenal insufficiency may be weak or absent (3). The percentage of patients with adrenal failure is considerably higher than in bilateral adrenal metastases from carcinoma (3–8%) (4). Cytokine-driven paracrine effects of lymphoma cells on adrenal gland microenvironment is suggested. The exact mechanisms are uncertain. Adrenal insufficiency in metastatic carcinoma is thought to reflect tumor replacement of functional tissue and interruption of vascular supply rather than cytochemical effects.

We present two cases of primary adrenal lymphoma manifesting as adrenal insufficiency with bilateral adrenal masses. One of the patients experienced almost total regression of the masses on treatment with standard replacement therapy alone, before subsequent aggressive regrowth. The other was biopsied during primary evaluation and responded to a combination of cytostatic therapy and radiation. Both patients presented with adrenal failure at an older age than expected for autoimmune adrenalitis. Negative 21-hydroxylase antibodies raised suspicion of an uncommon cause, and both had adrenal lesions pointing toward malignant disease. Adrenal lesions may have several causes, and biopsy should be taken when pheochromocytoma is biochemically excluded. The possible tumor-reducing effect of replacement therapy in one of our cases confused and delayed the diagnostics. Glucocorticoids are part of the standard regimen for several lymphoid cancers, due to steroid sensitivity of tumor cells that seems to be more pronounced for immature lymphoid cells (4). Glucocorticoids have direct actions on gene transcription through glucocorticoid response elements (GREs) and indirect actions through interaction with transcription factors. Effects on immune cells include inhibition of nuclear factor kappa B (NF-κB) and AP-1 (5, 6). NF-κB is a transcription factor for cytokines and genes involved in lymphocyte development, inflammatory response and apoptosis. AP-1 is also a proinflammatory transcription factor (6). In our case number two, tumor regress was seen shortly after starting cortisone replacement therapy. Because of the strong correlation in time between treatment initiation and tumor shrinking, steroid sensitivity rather than spontaneous recovery seems to explain the regression. Obviously, this postulation will never be confirmed. Supporting our theory, there are no previous reports describing spontaneous regression of primary adrenal lymphoma. Initial recovery might be explained by primary indolent tumor histology transforming into a more aggressive type. In lack of biopsy, this hypothesis will remain unconfirmed. Diffuse large B-cell lymphoma has a reported 3-, 6- and 12-month survival of 67, 46 and 20%, respectively (3). As described in the section on 'Case presentations', one of our patients died of CNS-lymphoma 9 years after first presentation. The other one had no clinical signs of recurrence at the last follow-up at the haematology outpatient clinic. It is now nearly 3 years after first presentation and about 2 years after diagnosis of diffuse large-cell B-cell lymphoma and initiation of chemotherapy.

Conclusions

Primary adrenal failure with negative 21-hydroxylase antibodies should be evaluated radiologically. As outlined in the European guidelines on adrenal nodules (7), patients with adrenal lesions should be discussed in a multidisciplinary team if imaging is not consistent with benign etiology. In general, biopsy is not recommended as part of diagnostic work-up unless there is a history of extra-adrenal malignancy. Lymphoma and infiltrative/infectious processes are mentioned as potential differential diagnoses where biopsy has a role in evaluation. Adrenalectomy is considered a better option than biopsy in most cases. Bilateral adrenal masses should be evaluated in the same way as unilateral lesions with separate characterization of each lesion. Given the high proportion of bilaterality and adrenal insufficiency in primary adrenal lymphoma, we find it reasonable to perform biopsy in patients with both characteristics when pheochromocytoma is excluded biochemically. Biopsy should be performed quickly to avoid potential steroid influences.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding
This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Patient consent
The authors confirm that they have obtained written informed consent from the patients for publication of this article and accompanying images.

Author contribution statement
K G wrote the first draft of the manuscript and did the review of the patient 1 and the literature search. E S H and K L did the review of the case 2. B D K is responsible for the x-rays. The other authors listed have actively contributed to the manuscript and approved the submission of this version of the manuscript.

References

1 Sævik ÅB, Akerman AK, Grønning K, Nermoen I, Valland SF, Finnes TE, Isaksson M, Dahlqvist P, Bergthorsdottir R, Ekwall O, *et al*. Clues for early detection of autoimmune Addison's disease - myths and realities. *Journal of Internal Medicine* 2018 **283** 190–199. (https://doi.org/10.1111/joim.12699)
2 Erichsen MM, Lovas K, Skinningsrud B, Wolff AB, Undlien DE, Svartberg J, Fougner KJ, Berg TJ, Bollerslev J, Mella B, *et al*. Clinical, immunological, and genetic features of autoimmune primary adrenal insufficiency: observations from a Norwegian Registry. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 4882–4890. (https://doi.org/10.1210/jc.2009-1368)
3 Rashidi A & Fisher SI Primary adrenal lymphoma: a systematic review. *Annals of Hematology* 2013 **92** 1583–1593. (https://doi.org/10.1007/s00277-013-1812-3)
4 Tallis PH, Rushworth RL, Torpy DJ & Falhammar H Adrenal insufficiency due to bilateral adrenal metastases - a systematic review and meta-analysis. *Heliyon* 2019 **5** e01783. (https://doi.org/10.1016/j.heliyon.2019.e01783)
5 McKay PaJAC LI Corticosteroids in the Treatment of Neoplasms. Holland-Frei Cancer Medicine. 6th ed. Hamilton, ON: BC Decker, 2003. (available at: https://www.ncbi.nlm.nih.gov/books/NBK13383).
6 Melmed S, Polonsky K, Larsen RP & Kronenberg H The adrenal cortex. In *Williams Textbook of Endocrinology*. 12th edition, 2011; Chapter 15, pp. 488–490 and 495, Saunders.
7 Fassnacht M, Arlt W, Bancos I, Dralle H, Newell-Price J, Sahdev A, Tabarin A, Terzolo M, Tsagarakis S & Dekkers OM Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. *European Journal of Endocrinology* 2016 **175** G1–G34. (https://doi.org/10.1530/EJE-16-0467)

Received in final form 17 December 2019
Accepted 14 February 2020