be detected later than the skin reaction. DRESS can mimic many diseases, particularly Stevens–Johnson syndrome. To estimate the probability for diagnosis the RegiSCAR [2] scoring system has been proposed (Table 1); like Bocquet's criteria diagnostic sensitivity is 96.6%. Pathophysiological hypothesis is hypersensitivity reaction with hypogammaglobulinaemia and subsequent CD8 T-cell response often combined with HHV-6, CMV, EBV reactivation [1,3,4] or EBV, CMV primoinfection. Association with HLA-B*5801 and possible familial aggregation is controversially discussed.[5] Allopurinol-induced DRESS is a supposed hypersensitivity reaction caused by detoxification defect with accumulation of oxypurinol.[1,6] Almost 50% of DRESS show involvement of at least one mucosal area and 1/3 facial oedema. 12% of skin rashes change into exfoliative dermatitis.[7] Lymphocyte-stimulation test can confirm T-lymphocytes proliferation (sensitivity 60–70%), skin biopsy mainly shows lymphocyte infiltration of the dermis with denser eosinophils than other drug reactions. DRESS can lead to lethal complications, mainly hepatic failure due to liver necrosis. Increased mortality was associated with heart rate >90/min, leucocytes >12 G/L, respiratory rate >20/min at beginning of, gastrointestinal bleeding, SIRS and coagulopathy during hospitalization and eosinophilia (>20%), atypical lymphocytosis (>10%) during maximal stage disease.[4,8] As early prognostic factor, fatal cases were associated with higher creatinine and ferritin levels.[4] Complications of DRESS include eosinophilic pneumonitis and myocarditis, leading to biventricular heart failure (mortality >50%). Hypothyroidism can emerge as late complication after 2–3 months. DRESS due to allopurinol seems to have more renal involvement and higher mortality rate compared to other drugs (18–25%).[2] Crucial therapeutic step is discontinuation of the culprit drug. No randomized controlled trials exist comparing supportive care versus systemic steroids. Steroids are mostly administered (0.5–1 mg/kg/day). Rapid tapering leads to relapse of symptoms; therefore slow dose reduction is advised.[2] Pulsed intravenous methylprednisolone seems to be efficient,[9] in contrast to intravenous immunoglobuline (IVIG),[5] although no controlled studies for IVIG exist for DRESS. Relapses as incomplete DRESS caused by structurally unrelated culprit drugs are frequently described.[10]

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Corticotrophin-releasing hormone (CRH) expression in the dermoid component of ovarian teratomas

Editor

CRH production has been demonstrated in normal skin, melanoma, squamous cell carcinoma and basal cell carcinoma. This is part of a dermal microcosm of the hypothalamic-pituitary-adrenal axis replete with CRH-receptors, adrenocorticotrophin hormone, alpha-melanocyte-stimulating hormone, melanocortin receptors, the glucocorticoid receptor and negative feedback loops.[1] In addition, upregulation of skin CRH has been implicated in non-malignant dermopathies including acne vulgaris[2] and psoriasis.[3] Though ovarian teratomas frequently contain skin elements, CRH production has never been investigated in these tumours to the best of our knowledge.

Herein, we report a novel finding of CRH expression in the dermoid component of ovarian teratomas from a young woman suspected of ectopic CRH syndrome. ACTH-dependent pituitary hypercortisolism was diagnosed, however, she failed to respond

to two trans-sphenoidal resections which both only demonstrated pituitary hyperplasia. As she had a history of recurrent bilateral ovarian teratomas and residual cystic masses on pelvic ultrasound, we performed immunohistochemistry of her previously resected teratoma specimens looking for a cause of hypercortisolism and pituitary hyperplasia. The tumours were negative for ACTH, but positive for CRH in the dermoid component (Fig. 1). CRH localised to the nucleus as has been reported in studies of human keratinocytes and T lymphocytes as well as preproCRH-transfected CHO-K1 ovary fibroblasts.[4] Such nuclear expression may indicate autocrine CRH effects consistent with the functional independence of the dermal HPA axis equivalent,[1] however, further study is required to support this hypothesis.

As the CRH staining was confined to dermal elements, it was considered insufficient to account for the patient's hypercortisolism which was largely unchanged by ovarian cystectomy. Later retrospective review of the intraoperative pituitary smears revealed adenoma, favouring Cushing's disease. Persistence of hypercortisolism was probably due to occult cavernous sinus disease evident on repeat imaging. Nonetheless, corticotroph adenomas have been seen on a background of corticotroph

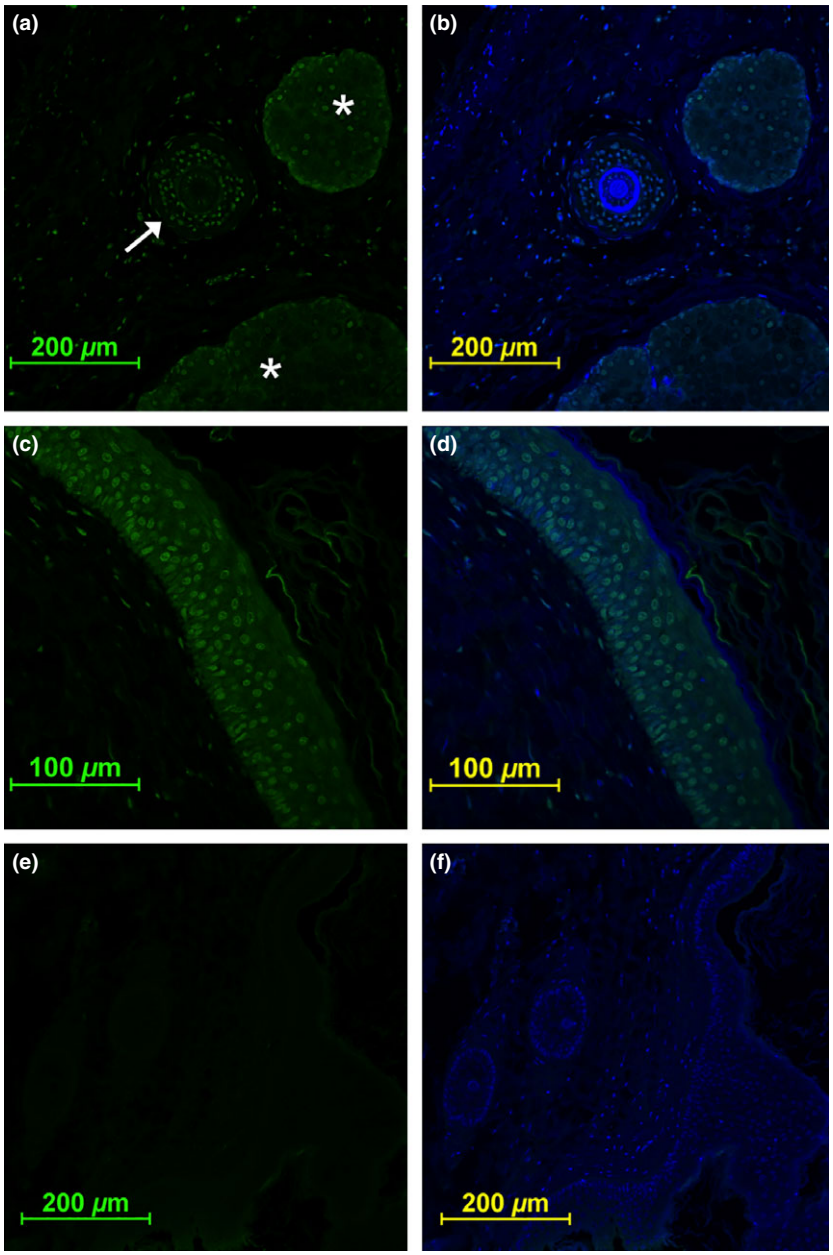

Figure 1 Confocal microscopy with human CRH antibody was positive in hair follicles (a, arrow), sebaceous glands (a, asterisks) and epidermal layers (c). Co-staining with DAPI demonstrated CRH localization to the nucleus (b, d). Rabbit IgG was used alone and with DAPI as negative controls (e, f). CRH expression in the setting of hypercortisolism was particularly remarkable as glucocorticoids downregulate local CRH production in studies of skin tissue.[1]

hyperplasia in autopsy studies.[5] It is possible that ectopic CRH production in our case led to a pituitary hyperplasia-adenoma sequence whereby autonomous ACTH production might have accounted for ongoing hypercortisolism despite resection of the teratomas. In any case, our discovery that teratomas are capable of producing CRH suggests it may be causative in other cases.

Our finding is particularly significant given the shared demographic of ovarian teratomas and endogenous hypercortisolism which predominate in young women. Whilst ectopic CRH syndrome due to ovarian teratomas has never been reported, such cases may have been overlooked. In the few reported cases of ectopic ACTH syndrome secondary to ovarian teratomas,[6] CRH staining was not performed thus it is unknown if CRH production was contributory. Indeed, concurrent ectopic ACTH and CRH production by other tumours is an established cause of hypercortisolism.[7] In addition to tumour immunohistochemistry, preoperative plasma CRH may be useful as this should be suppressed in primary ACTH-mediated hypercortisolism.

Even in the absence of Cushing's syndrome, CRH production by the dermoid component of ovarian teratomas may have reproductive consequences as normal ovaries express CRH and CRH-receptors which mediate pro- and anti-ovulatory paracrine effects. The anti-ovulatory effect is mediated by dose-dependent CRH-induced inhibition of oestrogen and progesterone production in human granulosa cell lines.[8] Heightened local expression of CRH by ovarian teratomas may thus contribute to inhibition of steroidogenesis thereby reducing fertility.

Local CRH excess might also participate in teratoma persistence and progression as *in vivo* studies have demonstrated accelerated tumorigenesis and increased blood vessel density in CRH-secreting human epithelial cell lines compared to clones that do not secrete CRH.[9] Another study demonstrated CRH production to be directly proportional to the aggressiveness of skin tumours with the greatest CRH expression found in malignant melanoma cell lines and the lowest in basal cell carcinoma lines.[10] As primary malignant melanoma has arisen within ovarian teratomas,[11] investigation is warranted into the oncogenic properties of CRH in ovarian teratomas analogous to the pre-existing skin models. Advances in our understanding of the skin biology within teratomas, as highlighted by this case, will further elucidate the role of skin as an endocrine organ.

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Syndrome of inappropriate secretion of antidiuretic hormone in a patient with drug-induced hypersensitivity syndrome

Editor

Drug-induced hypersensitivity syndrome (DIHS)/drug rash with eosinophilia and systemic symptoms (DRESS) is a severe multi-organ reaction related to drugs and to reactivation of herpes viruses, particularly HHV6. The most frequent incriminated drugs are the aromatic anticonvulsants and sulphonamides.[1] Symptoms typically develop 4–6 weeks after the administration of the causative drug and include fever, maculopapular rash, facial oedema, leucocytosis with eosinophilia along with visceral