Case report

Sylvia Damen

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Saas Fee

48 year old woman

- History: maxillary sinusitis and otitis media
- Anamnesis: nausea, vomiting, malaise, weight loss, secondary amenorrhea
- Physical examination: no abnormal findings
- Laboratory tests:
  - CRP 51 mg/L (< 10), ESR 90 mm/h (< 19), Na 150 mmol/l (135-145)
  - Calcium 2.97 mmol/l (2.10–2.55), PTH 1.3 pmol/l (1.3–6.8)
- During admission polyuria and polydipsia
  - Na 162 mmol/l
  - Osmolality serum 354 mOsm/kg
  - Osmolality urine 128 mOsm/kg

Differential diagnosis

- Nausea, vomiting, malaise, weight loss, inflammation
  - Infectious disease
  - Systemic disease
    - Granulomatous: tuberculosis, sarcoidosis, ANCA-associated vasculitis
  - Malignancy / Lymphoma
- Hypernatraemia
  - Dehydration / negative fluid balance
  - Diabetes insipidus: central vs nefrogenic
- Hypercalcaemia with low-normal PTH
  - Osteolytic ossal metastases, PTH-related peptide producing carcinoma, vitamine D intoxication or overproduction

- Chest radiography and CT: multiple pulmonary infiltrates

- Granulomatous disease?
  - Tuberculin skin test: negative
  - ACE concentrations: normal
  - c-ANCA 1:128, PR3-ANCA+

Hypernatraemia

- Diabetes insipidus; central cause
  - high plasma osmolality, low urine osmolality
  - undetectable low antidiuretic hormone (ADH)
- Screening other hormonal axes
  - hypogonadotropic hypogonadism (LH < 0.1 IU/L, FSH 1.2 IU/L)
  - mild hyperprolactinaemia (1.36 U/L) (0.10-0.64)
  - ***primary hyperthyroidism***
    - thyrotropin 0.006 mU/L (0.4-3.5), free thyroxine 24.2 pmol/L (8-18)
- MRI brain
  - diffuse enlarged pituitary gland with a swollen stalk

Fluoro-D-Glucose (FDG) PET CT

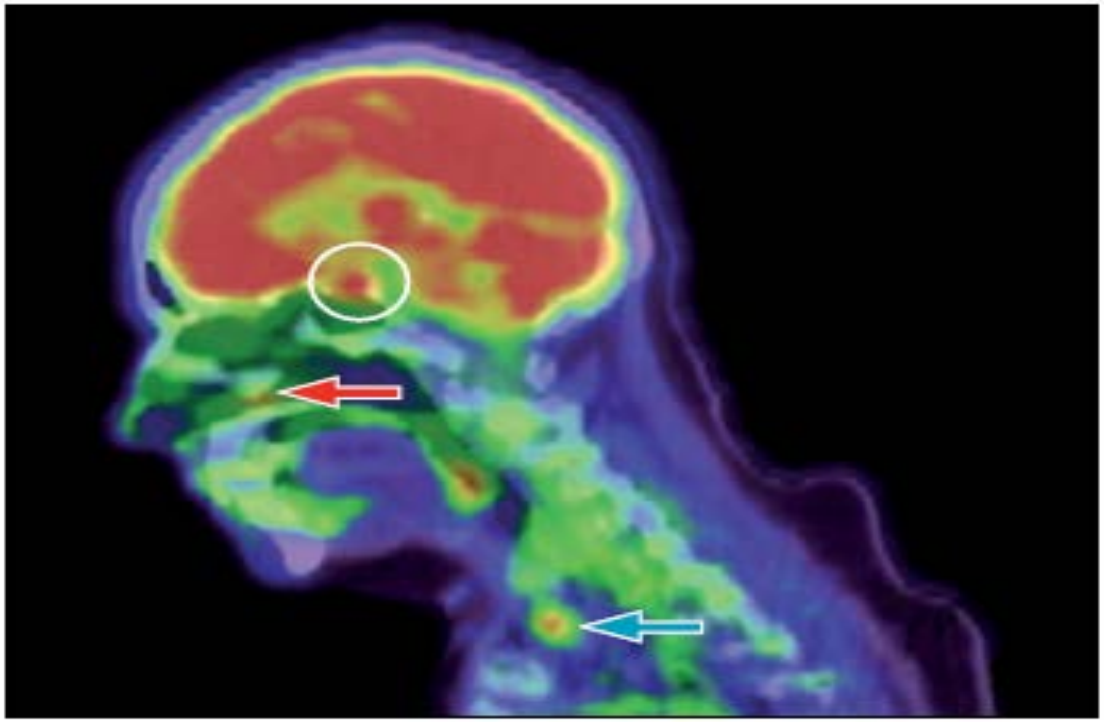
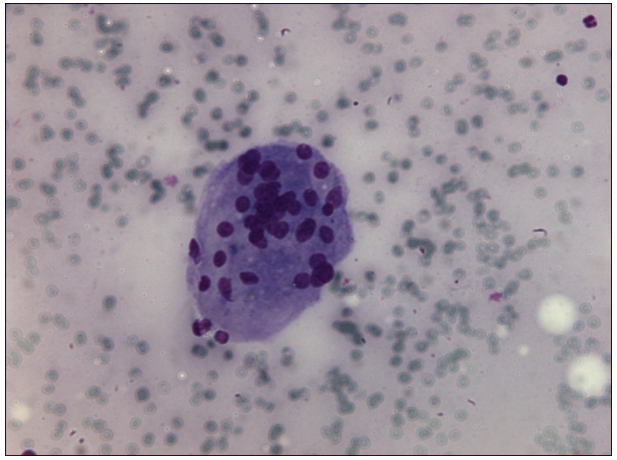


Figure: **FDG-PET-CT scan**
Abnormally increased FDG uptake in the pituitary gland (circle), the left nostril (red arrow) and in the left lobe of the thyroid gland (blue arrow). Other areas of high uptake are physiological (oropharyngeal and brain).

Pathology

- Nasal biopsy (septum): aspecific chronic inflammation with ulcerations
- Bronchus biopsy: aspecific inflammation
- Fine-needle aspiration thyroid lesion: inflammation with giant cells



Hypercalcaemia

- 25(OH) vit D 29 nmol/l (>70)
- 1,25(OH)2 vit D 105 pmol/l (50-110)
- PTH 1.3 pmol/l (1.3–6.8)

- Extra-renal production 1,25 dihydroxycholecalciferol
  - known complication of granulomatous disease
  - production by inflammatory cells
    - macrophages, T-cells

Conclusion

- Diagnosis: granulomatosis with polyangiitis (Wegener's granulomatosis) with
  - nasal involvement
  - pulmonary involvement
  - pituitary involvement: hypophysitis
    - central diabetes insipidus, hypogonadotropic hypogonadism, hyperprolactinaemia
  - probable thyroidal involvement
    - FDG-PET positive lesion left lobe with thyrotoxicosis

Treatment

- 1000 mg methylprednisolone iv during 3 days
- Followed by
  - Oral prednisolone 1 mg/kg/day, tapering dose
  - Oral cyclophosphamide 2 mg/kg/day
- Desmopressin (central diabetes insipidus)

- Follow-up
  - Thyroid dysfunction and hypercalcaemia soon resolved after initiating treatment
  - Recovery sinusitis
  - Disappearence diabetes insipidus
  - Negative PR3-ANCA

Discussion

- Granulomatosis with polyangiitis
- Disease: systemic necrotising vasculitis predominantly involving upper airways, lungs, kidney's. Initial fase: granulomatous
- Rare endocrine involvement, both pituitary gland and thyroid
- First case-report with both involvements

Take home message

- Granulomatosis with polyangiitis (Wegener’s granulomatosis) can present with a combination of endocrine abnormalities and inflammation

Case Report

Multiple endocrine abnormalities

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In September, 2008, a 48-year-old woman was admitted because of nausea, vomiting, and malaise. She had a history of maxillary sinusitis and otitis media. Physical examination was normal. Laboratory tests showed increased concentrations of inflammatory markers (CRP 51 mg/L, ESR 90 mm/h), hypernatraemia (150 mmol/L), and hypercalcaemia (2·97 mmol/L, PTH 1·3 pmol/L). Central diabetes insipidus was confirmed by high plasma osmolality and undetectable ADH. All other hormonal axes were tested and showed hypogonadotropic hypogonadism (LH <0·1 IU/L, FSH 1·2 IU/L), mild hyperprolactinaemia (1·36 U/L), and, surprisingly, primary hyperthyroidism (thyrotropin 0·006 mU/L, free thyroxine 24·2 pmol/L). MRI of her brain showed a diffuse enlarged pituitary gland with a swollen stalk.

Because chest radiography and CT showed multiple pulmonary infiltrates, we suspected a granulomatous disease. Tuberculin skin test was negative, ACE concentrations were normal, but antineutrophil cytoplasmatic antibodies (ANCA) were positive (c-ANCA 1:128, PR3-ANCA). Fluoro-D-Glucose (FDG)-PET-CT showed increased FDG uptake in the pituitary gland, left nostril, and left lung, and a focal active lesion in the left lobe of the thyroid gland (figure). Nasal biopsy showed active, chronic ulcerative inflammation. Fine-needle aspiration of the thyroid lesion showed inflammation with giant cells. A diagnosis of granulomatosis with polyangiitis (Wegener's granulomatosis) with pulmonary, nasal, pituitary, and probable thyroidal involvement was made. We treated our patient with 1000 mg methylprednisolone intravenously (3 days), followed by oral prednisolone (60 mg, tapering dose), and oral cyclophosphamide (2 mg/kg per day). Central diabetes insipidus was treated with oral desmopressin. There was no clinical need for oestrogen supplementation. Thyroid dysfunction and the hypercalcaemia resolved soon after initiation of treatment. When last seen in May, 2011, she was in a good clinical condition without relapse.

Pituitary insufficiency due to hypophysitis as the first presentation of granulomatosis with polyangiitis is rare and therefore not the first diagnosis that came to mind with our patient. The presence of pituitary-stalk thickening is the most striking radiological feature of an inflammatory process involving the pituitary gland.[1] The extent of pituitary involvement in granulomatosis with polyangiitis is variable. Diabetes insipidus is the most common endocrine abnormality.[1] In our patient, there was also hypogonadotropic hypogonadism. The mild hyperprolactinaemia was probably because of compression of the infundibulum accompanying hypophysitis. The diagnosis was made on the basis of clinical manifestations in the presence of PR3-ANCA.[2] In an effort to obtain histopathology, FDG-PET-CT was done to identify other biopsy sites, because the pulmonary lesions as well as the pituitary gland were not readily accessible. Granulomatosis with polyangiitis is a systemic necrotising vasculitis predominantly involving the upper airways, lungs, and kidneys. In its initial phase it can be purely granulomatous, as in our patient, as suggested by the MRI and the nasal biopsy.[3] Hypercalcaemia is a known complication of granulomatous diseases. It is generally due to excessive synthesis of 1,25-dihydroxycholecalciferol by inflammatory cells.[4] Although the presence of giant cells, found by cytological investigation of the thyroid gland in our patient, is a well known abnormality,[5] the accompanying primary hyperthyroidism is less well described. Our patient demonstrates the importance to think laterally in the presence of multiple endocrine abnormalities and high concentrations of inflammatory markers.

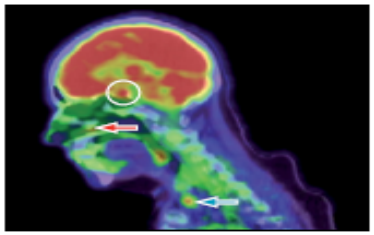

Figure: FDG-PET-CT scan
Abnormally increased FDG uptake in the pituitary gland (circle), the left nostril (red arrow) and in the left lobe of the thyroid gland (blue arrow). Other areas of high uptake are physiological (oropharyngeal and brain).

Contributors
CvD, JK, PvP, RvR, and JWCT cared for the patient. CvD, JK, and JWCT wrote the report. Written consent to publish was obtained.

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