A woman in her thirties with breast cancer and bilateral goitre

When patients have symptoms stemming from different organ systems, several specialists will often be involved in their treatment. Interdisciplinary thinking may be crucial for early diagnosis and life-saving prophylaxis.

A woman in her late thirties was electively hospitalised on suspicion of a locally advanced carcinoma of the right breast. Her medical history showed that she had had type 1 diabetes mellitus since she was 11 and had been found to have an extra, non-functioning renal system. A couple of years previously, ultrasound and CT throat had been used at a local hospital to examine her for bilateral goitre. The conclusion of these tests was colloid nodular goitre with no suspicion of malignancy. There is no information as to whether cytology tests were carried out. The patient had two children. Several of the patient’s maternal aunts and uncles had died of cancer.

Suspicion of locally advanced carcinoma of the right breast arose following mammography conducted by a private X-ray institute. The patient suffered from breast tenderness and had requested the examination. The examination of breasts and axillae revealed possible malignant changes in the right breast, possible lymph node metastasis in the right axilla and non-specific changes in the left breast. The radiological diagnosis was regarded as certain, and the patient was referred directly for hospitalisation. Biopsies were taken in connection with hospitalisation to examine her for bilateral goitre. The conclusion of these tests was colloid nodular goitre with no suspicion of malignancy. There is no information as to whether cytology tests were carried out. The patient had two children. Several of the patient’s maternal aunts and uncles had died of cancer.

A cytological sample from a radiologically benign-seeming lesion in the left mamma revealed papillary cell groups without atypical signs. No biopsy was taken from this lesion. A further X-ray examination of the thyroid yielded an image consistent with nodular colloid goitre, but cytological samples contained too little material and were non-diagnostic. The patient received pre-operative chemotherapy and lost her hair. It proved difficult to find a wig that was large enough for her head. Seven months after the start of chemotherapy, ablation of the right breast was performed with subsequent post-operative radiotherapy.

Findings of synchronous tumour-like changes in the breasts and thyroid lobes of young people are unusual. When malignant neoplasms are found in one of these organs, it is important to determine whether tumours found in the second organ represent metastasis or a new primary tumour, because it may have consequences for treatment.

Because of pressure symptoms in the throat and respiratory discomfort, a further radiological examination was made of the thyroid, and cytological samples obtained, but these too failed to provide sufficient material for diagnosis. The patient’s left thyroid lobe was removed the year after she was treated for cancer of the right breast, although there was no preoperative cytological diagnosis. A macroscopic examination of the left thyroid lobe revealed multiple tightly packed nodules (Fig. 1). A histological examination revealed an unusual image with tightly packed follicular adenomas and adenomatous colloid nodules (Fig. 2). The changes are consistent with findings in the literature described as characteristic of Cowden’s syndrome (CS), which is a dominant hereditary condition characterised by multiple benign and malignant neoplasms and hamartomas. The histology report indicated that the image could suggest Cowden’s syndrome, and the patient was referred for genetic testing. The same year as the left thyroid lobe was removed, a cavernous haemangioma was also removed from the skin of the left thigh.

The phosphatase and tensin homologue gene, PTEN, is a tumour suppressor gene and plays a central part in controlling cell proliferation, differentiation and apoptosis (1). Mutation of the gene contributes to increased cellular proliferation, and somatic mutations of the PTEN gene are associated with a number of different types of cancer (2, 3). PTEN hamartoma tumour syndromes (PHHTS) are rare, hereditary conditions and due to germline mutations in the PTEN gene. The condition includes Cowden’s syndrome, Bannayan–Riley–Ruvalcaba syndrome (BRRS), Proteus syndrome and Proteus-like syndromes and autism spectrum disorders associated with macrocephaly (4).

About two years after she had been found to have mammary carcinoma, the patient
arrived with her mother for genetic counsel-
ing. Her mother related that the patient had
been sick a great deal as a child. She was
found to have nasal polyps during her child-
hood. She had a tonsillectomy and appen-
dectomy, and was found to have diabetes mellitus. Her mother related that the patient
had always had a large head, which was
noticed for the first time when she was a
newborn baby. The patient was monitored
for a year on this account. The assessment
during her childhood ruled out hydrocepha-
lus as the cause of her large head circumfer-
ence. The large circumference could be the
reason why it was difficult to find a wig large
enough for the patient's head in connection
with her chemotherapy.

It emerged that the patient had been
referred for genetic evaluation 12 – 13 years
previously because of a history of breast and
ovarian cancer in her mother’s family. At
that time the patient did not have cancer.
Nor did her mother have cancer, and there
was no indication for further genetic evalua-
tion and testing. At that time, genetic testing
options were relatively limited, and testing
for PTEN gene mutation was not offered.
The patient's father died when he was in his
mid-fifties, but not of cancer.

In connection with the genetic counselling
for which she was referred on account of sus-
pected Cowden's syndrome, skin manifesta-
tions were detected that were characteristic
of PTEN mutation (papillomas and trichilem-
momas). The genetic test revealed a mutation
of the PTEN gene. This, coupled with the clin-
ical picture, fitted Cowden’s syndrome.

Cowden's syndrome is a dominant heredi-
tary condition characterised among other
things by numerous hamartomas, which
represent overgrowth of tissue components
that should normally be present at the local-
ity in question. Skin changes may consist of
papillomas in the mucous membrane of the
mouth and on the tongue, trichilemmomas,
most frequently on the face, particularly
around the nose, eyes and mouth, and/or
thickened skin on the hands and feet, so-cal-
led acral keratosis (5, 6). Haemangiomas,
lipomas and neurofibromas are also com-
mon. Benign changes in the thyroid (colloid
nodules, adenomas), breast (fibroadenomas,
fibrocystic changes) and intestines (hamar-
tomas, ganglioneuromas) occur frequently
(5, 6). Almost all individuals with Cowden’s
syndrome have a head circumference larger
than the 97.5 percentile (7). Macrocephaly
in connection with Cowden’s syndrome is
probably secondary to megencephaly (7).
Many individuals with the syndrome have
learning disabilities, some have impaired
mental capacity and also motor changes.
Individual variation is substantial (5, 6).

There is a substantially elevated risk of
cancer, the most prevalent types being breast,
thyroid, uterine and renal cancer (8).

It is usually assumed that more than 90 %
of individuals with Cowden’s syndrome pre-
sent with the phenotype in their twenties. The
diagnostic criteria for the syndrome have
been revised several times (6, 9) (Box 1).

Further genetic tests were conducted on the
family. The patient’s mother was tested, but
she did not have a genetic defect in the PTEN
gene. Because of the maternal family history
of breast and ovarian cancer, an analysis
was performed of her BRCA1 and BRCA2
genes, which did not reveal a mutation. The
possibility that the PTEN genetic defect
stemmed from the patient’s deceased father
cannot be dismissed. Alternatively, it may
have arisen de novo in the patient.

After being assessed by a medical geneti-
cist, the patient was referred for examina-
CASE REPORT

Multiple trichilemmomas (multiple mucocutaneous lesions: women, 60 cm for men
Oesophageal glycogen acanthosis (Bowel cancer
Minor criteria
Oral papillomas (Minor criteria
Intellectual disability (IQ
Multiple palmoplantar keratoses (nodular goitre
Other thyroid lesions, e.g. adenomas, neoplasms
Renal cell carcinoma
Vascular anomalies

Discussion
Cowden’s syndrome is named after Rachel Cowden, the first patient who was described as having many of the characteristic changes found in this patient group (10). Cowden’s syndrome is rare. A Dutch clinical epidemiological study from 1999 estimated its prevalence to be between 1:200,000 and 1:250,000 (11), but as the syndrome has a variable clinical presentation and is often difficult to recognise, this is believed to be an underestimation (9). Increased possibilities for genetic testing may help to determine the prevalence of the disease, also in subjects who do not meet the classical clinical criteria. It is estimated that 10–47% of persons with PTEN mutation have a de novo mutation (12), i.e., neither of the patient’s parents has the mutation.

The great variation in clinical expression of Cowden’s syndrome makes diagnosing it a challenge. Not all patients found to have a defective PTEN gene meet the clinical criteria for the syndrome. Similarly, there may be patients who meet the clinical criteria for Cowden’s syndrome, but who do not have a detectable PTEN gene mutation (13). Many features of Cowden’s syndrome are subtle and occur frequently in the general population. Clinical findings in various organs such as the skin, thyroid, breast, bowel, central nervous system and soft tissue, including the vascular and urogenital systems, result in patients being attended to by a variety of medical specialists, with a risk of the overall picture not being seen. Dermatologists are often the first to meet patients with the syndrome (14, 15). Detection of a PTEN mutation makes it possible to treat premalignant conditions and thereby improve survival. The patient’s relatives (parents, siblings and children) should be offered genetic testing. In rare cases, children with PTEN gene defects may develop cancer in addition to benign nodules in the thyroid gland (8). It is therefore permissible to test children for this defect. In the event of findings of multiple mucocutaneous papules in young patients, Cowden’s syndrome should be ruled out. Breast and endocrine surgeons who treat breast and thyroid lesions should also have

BOX 1
Clinical criteria for Cowden’s syndrome
The patient must meet ≥ three major criteria, one of which must be macrocephaly, Lhermitte-Duclos disease or gastrointestinal hamartomas, or two major and three minor criteria. The box is modified from Pilarski et al. (6).

Major criteria
Breast cancer
Endometrial cancer, epithelial
Thyroid cancer, follicular
Gastrointestinal hamartomas, incl. ganglion-neuromas, excl. hyperplastic polyps, ≥ 3
Lhermitte-Duclos disease, adult
Macrocephaly, ≥ 97th percentile: 58 cm for women, 60 cm for men
Macular pigmentation of glans penis
Multiple mucocutaneous lesions: Multiple trichilemmomas (≥ 3, at least one verified by means of biopsy)
Multiple palmpoplantar keratoses (≥ 3)
Mucocutaneous neuromas (≥ 3)
Oral papillomas (≥ 3)

Minor criteria
Autism spectrum disorder
Bowel cancer
Oesophageal glycogen acanthosis (≥ 3)
Lipomas (≥ 3)
Intelectual disability (IQ ≤ 75)
Renal cell carcinoma
Testicular lipomatosis
Thyroid cancer, papillary or follicular
Other thyroid lesions, e.g. adenomas, nodular goitre
Vascular anomalies

Recommended checks
The box is modified from Tan et al. and Gammon et al. [8, 13]
Annual thyroid ultrasound is seldom relevant before the age of ten. Prophylactic thyroidectomy can be considered if it is difficult to assess the gland because of multiple nodules.
Annual mammography and MRI scan of the breasts from the age of 25. Prophylactic mastectomy should be considered.
Annual uterine screening with ultrasound and possibly endometrial cytology tests from the age of 30.
Basic cutaneous examination after genetic testing. Follow-up as needed or about every fifth year.
Annual renal ultrasound from the age of 40.
Colonoscopy every five years from the age of 40.

Cowden’s syndrome in mind as a possible diagnosis
Pathologists have a key and vital part to play in detecting the syndrome (16). New and improved pathology databases with an overview of all specimens submitted for testing from each patient have given pathologists an important diagnostic means of identifying patients who should be tested for PTEN mutation. From a histopathological point of view, findings of a large number of tightly packed follicular adenomas and adenomatous colloid nodules should result in a remark in the results urging clinicians to consider referral for genetic study with Cowden’s syndrome in mind. Follow-up is recommended for patients in whom PTEN mutation is detected with a view to preventing malignant neoplasms or detecting neoplasms at an early stage. Guidelines for follow-up have changed over time, and vary somewhat across institutions. As a result, we have established guidelines during the past few years (8, 13) (Box 2).

The patient presented in this case history had a complex of clinical symptoms and findings for several years without their arousing suspicion of a genetic connection. The pathologists reacted to the histological appearance of the thyroid specimen, as a result of which the patient was referred for genetic study. Knowledge of, and focus on Cowden’s syndrome has been increasing both in Norway and internationally over the past ten years, not least as a result of steadily...
improved multidisciplinary cooperation. The patient in this case history developed her first symptoms many years before diagnostic criteria and follow-up for this rare disease had been established. Cowden’s syndrome was not mentioned in the patient’s therapy programmes from the period when she was diagnosed with breast cancer. According to today’s breast cancer treatment programme, the patient should have been referred for genetic study. Since histological findings for this patient led to genetic testing and detection of a PTEN mutation, several patients with a PTEN mutation have been found at the Department of Pathology, Oslo University Hospital, following findings of characteristic histological features in thyroid specimens.

When the patient in question was referred for genetic study 12–13 years earlier because of her family history, she had not yet been found to have cancer. This, coupled with the fact that the testing options were limited at that time, meant that there was no indication for further genetic study. In the case of this patient, early suspicion of Cowden’s syndrome on the part of one or more of the clinicians who treated the patient and subsequent genetic testing might have led to prevention or early diagnosis of her mammary carcinomas.

This case study shows that interdisciplinary cooperation on patients with a complex of symptoms and findings is important. Multidisciplinary meetings at which medical history, symptoms, and clinical, radiological and pathological findings are presented and discussed could contribute to syndromes like Cowden’s being detected so early that prophylactic measures can be implemented.

The patient has consented to the publication of the article.

Eva Sigstad (born 1966)
Specialist in pathology with special expertise in thyroid pathology.
The author has completed the ICMJE form and reports no conflicts of interest.

Krystyna Kotanska Grøholt (born 1954)
Specialist in pathology with special expertise in thyroid pathology.
The author has completed the ICMJE form and reports no conflicts of interest.

Kjersti Jørgensen (born 1972)
Genetic counsellor.
The author has completed the ICMJE form and reports no conflicts of interest.

Astrid Stormorken (born 1959)
Specialist in medical genetics.
The author has completed the ICMJE form and reports no conflicts of interest.

Henrik Stenwig Li (born 1971)
Specialist in ear, nose and throat diseases.
The author has completed the ICMJE form and reports no conflicts of interest.

References

Received 29 June 2016, first revision submitted 29 December 2016, accepted 18 April 2017. Editor: Lars Frich.