Hamartomas

A hamartoma is defined as a focal growth that resembles a neoplasm but results from faulty development in an organ. They can occur anywhere in the body. They have been described in many organs but especially the chest, breast, skin and brain. They are also reported in the eye, colon and liver.

It is important to note that:

- Hamartomas are a major feature of tuberous sclerosis.
- Hypothalamic hamartoma is a rare benign brain tumour located near the hypothalamus.
- Multiple hamartomas throughout the body occur in Cowden's disease. Most isolated hamartomas are benign but in Cowden's disease there is a risk that one or more may undergo malignant change.
- Multiple benign hamartomas are called Proteus' syndrome. The condition reached public attention in the film "The Elephant Man".

Epidemiology

Incidence

It is difficult to give an accurate assessment of incidence, as many skin lesions are simply ignored as 'birthmarks' and many internal lesions are incidental findings. Most cause no trouble but where they represent space-occupying lesions, especially in the brain, they have serious consequences.

- Uterine fibroids are a very common form of hamartoma.
- Cowden's disease is rare. 300 cases have been described worldwide.
- About 200 cases of Proteus' syndrome have been described worldwide.

Risk factors

- Cowden's disease and tuberous sclerosis are autosomal dominant conditions with an equal sex distribution.
- The genetics of Proteus' syndrome are less certain. It may be sporadic or autosomal dominant. It was thought to be due to mutations in the PTEN suppressor gene. However, recent research has identified a mutation affecting the production of AKT1 oncogene kinase, an enzyme involved in cell proliferation.

Presentation

Symptoms

- Symptoms depend upon the site of the lesion and they may present at any time from birth to middle age but usually early in life.
- There may be a disfigurement of the skin.
- It may be an incidental finding on CXR or mammography.
- In the brain they can cause epilepsy and mental impairment is common but not inevitable and varies in severity.

In hypothalamic hamartoma

- Epilepsy begins in infancy with gelastic or laughing seizures.
- Early childhood development is normal. The laughter is brief, frequent and mechanical in nature. It is often not recognised that the child is having a seizure and so the diagnosis is delayed.
- Between the ages of 4 and 10, the disorder becomes more ominous. The associated episodes of laughter develop into seizures that become longer, more severe and sound less natural. Secondary generalised epilepsy may appear.
Multiple seizures and progressive cognitive impairment occur. The child may show bouts of extreme rages, poor social adjustment and often precocious puberty.\[^{10}\]

**Signs**

**Skin and mucous membranes**
Papules of various types, fibromas, keratoses, café-au-lait patches and haemangiomas are all described.

**Chest**\[^{11}\]
- Hamartomas can on rare occasions present as a mass in the chest.
- The majority are peripheral and produce no symptoms but some produce respiratory symptoms, chronic cough and haemoptysis. A small number may grow slowly.
- They are unusual before the third decade.
- They appear on CXR as a 'coin lesion' that has to be differentiated from a granuloma or malignant neoplasm. They are discreet and often have calcification making them radio-opaque. They are usually less than 2 cm and composed mostly of benign cartilage.

**Breast**
- Hamartomas are an uncommon benign breast lesion composed of variable amounts of adipose, glandular and fibrous tissues.
- They are usually asymptomatic but may be palpable.
- Most occur in women aged over 35.
- A confident diagnosis can be made on mammography when the lesion has a classical appearance.

**Head and neck**
It may present as a swelling or lump in the head or neck, as pain in the chin, neck or face or as hoarseness.

**Gastrointestinal tract**
- Polyps can occur anywhere in the gut but are most common in the colon.
- The malignant potential of polyps is low, unlike familial polyposis coli.

**Differential diagnosis**
- Isolated lesions are usually excised and examined for histology to confirm their nature.
- The main concern is that the lesion may be malignant.
- The classical features of tuberous sclerosis are not always present, especially in the early years.
- Hypothalamic hamartoma is one of the few diseases to cause gelastic seizures. Others are temporal lobe epilepsy, infantile spasm, Angelman’s syndrome, hypothalamic gliomas and tumours of the third ventricle.

**Investigations**\[^{12}\]
- If an intracranial hamartoma is suspected, a positron emission tomography (PET)/CT or MRI scan is required.
- CT or MRI scanning of the chest, or mammography, may produce enough confidence in the diagnosis to remove the need for excision biopsy.\[^{13}\]
- Antenatal diagnosis by ultrasound of a thoracic mesenchymal hamartoma has been reported.\[^{14}\]

**Associated diseases**
- Tuberous sclerosis has many other features.
- In Cowden’s disease there is a risk of malignant change, especially producing breast cancer in women and follicular carcinoma of the thyroid in men.
Management

Management depends upon a firm diagnosis followed by appropriate action. Most isolated lesions can be ignored. If it is part of a syndrome like tuberous sclerosis or Cowden's disease the management is as for that disease.

Non-drug

Intracranial lesions may require management of developmental delay or behavioural problems.

Drugs

Epilepsy may need treatment.

Surgical

- Excision biopsy is often required for diagnosis. For skin lesions, chemical peels, laser resurfacing, surgery or shave excisions may be required.
- Hypothalamic hamartomas are usually benign but often associated with seizures which do not respond to medication and surgical removal may be required. The lesion usually straddles the optic nerve, making removal difficult. However, various approaches have been developed, including endoscopic surgery.\footnote{15} While the procedure is relatively safe, memory loss is a common complication in older adolescents and adults.\footnote{16}
- Pulmonary hamartomas can be removed using a thorascopic approach.\footnote{17}

Complications

- Malignant change is common in Cowden's disease.
- It is less common in tuberous sclerosis.
- In isolated lesions it is rare.

Prognosis\footnote{18}

In Cowden's disease:

- The lifetime risk of breast cancer is 85%.
- The lifetime risk of thyroid cancer is 35% (usually follicular but occasionally papillary).
- The lifetime risk of endometrial cancer is approximately 28%.
- One study has also reported a link with colorectal cancer.\footnote{19}

Further reading & references

- Cowden Syndrome 1, CWS1; Online Mendelian Inheritance in Man (OMIM).
18. Eng C; PTEN Hamartoma Tumor Syndrome (PHTS)

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