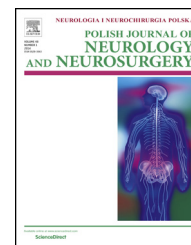


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## Case report

# Hypophyseal metastases: A report of three cases and literature review



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## ARTICLE INFO

## Article history:

Received 8 November 2015

Accepted 24 August 2016

Available online 4 September 2016

## Keywords:

Pituitary tumour

Metastases

Renal cell carcinoma

Lymphoma

Breast cancer

## ABSTRACT

Metastatic tumours to the pituitary gland are rare. The most frequent are metastases from breast and lung. We describe three patients with metastatic tumours: (I) a 54-year-old patient with metastatic renal clear-cell carcinoma and consequent disturbances in visual acuity, cranial nerve paresis and panhypopituitarism, (II) a 60-year-old patient with a diffuse large B-cell lymphoma with panhypopituitarism and diabetes insipidus and (III) a 57-year-old patient with metastasis of breast cancer and panhypopituitarism, visual impairment and cranial nerve paresis. A transnasal endoscopic biopsy and resection of the tumour was performed in all patients, followed by the oncological treatment. Despite the rarity of the disease, it is important to suspect a metastatic pituitary tumour especially in the case of diabetes insipidus, ophthalmoplegia, rapid course of the disease and headaches. In 20–30% of patients, a metastasis to the pituitary is the first manifestation of a tumour of unknown origin. Surgical and adjuvant therapy may improve the quality of life. The survival is not affected, however, and the prognosis of the disease is usually poor.

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## 1. Introduction

Metastatic pituitary tumours are rare complications of malignancy, representing only 1% of surgical tumours of pituitary gland. They are usually encountered in elderly patients with disseminated malignant disease [1,2]. The most frequent are metastases of breast and lung cancer. The

incidence of metastatic pituitary tumours is increasing in the last decade due to the improved diagnostics, advances in oncological treatment and longer survival of patients with malignant tumours [3]. In 20–30%, the metastatic tumour to pituitary may signify the first manifestation of a malignant tumour of unknown origin and therefore requires a comprehensive diagnostic workup. There are, however, no clear criteria to distinguish between a pituitary adenoma and a

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<http://dx.doi.org/10.1016/j.pjnns.2016.08.007>

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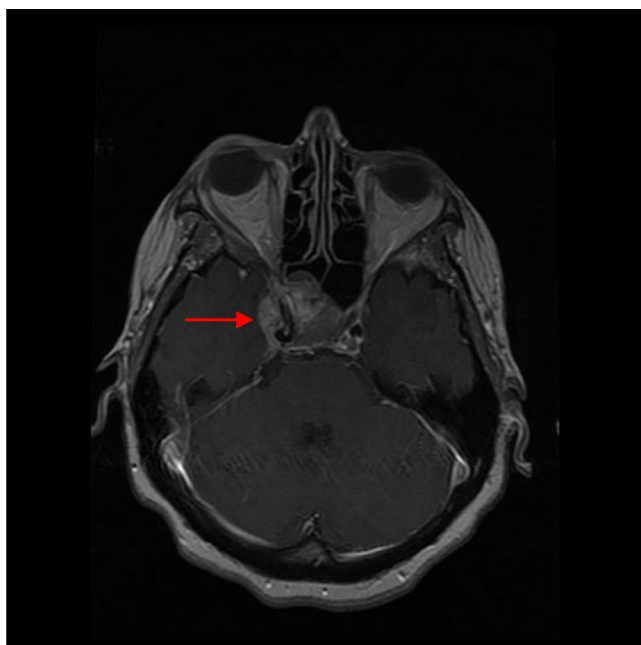
metastatic tumour [4]. This report illustrates three patients with metastatic tumours of various aetiologies to the pituitary gland. The biopsies and resections of the tumours were performed through a transnasal endoscopic approach.

## 2. Presentation of patients

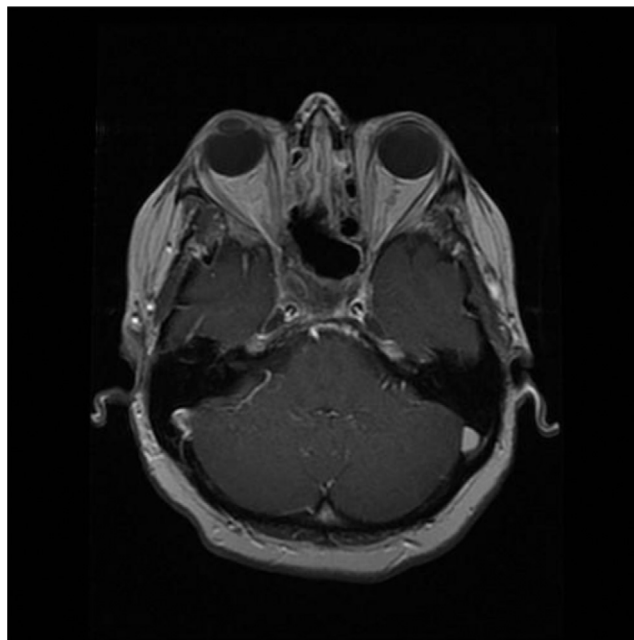
### 2.1. The first patient

In a 54-year-old lady, a nephrectomy due to a renal cell carcinoma was performed six years ago. After a period of stable clinical condition, the disease has eventually relapsed with fatigue, abdominal pain, general wasting and weight loss. The computer tomography (CT) of the chest and abdomen showed metastases in the pancreas and lungs. Three weeks before admission to the neurosurgical department, the patient has inadvertently lost 8 kg and started to experience a burning pain in the eyes and extensive lacrimation, followed by the right eyelid ptosis, worsening of visual acuity with double vision and headache. Imaging of the head showed a tumour in the pituitary gland of 2.5 cm in diameter with the destruction of surrounding bone and tumour invasion into the right parasellar space (Fig. 1).

In clinical examination, severe amblyopia was evident, more pronounced on the right eye (the visual acuity was 0.2 with right-sided visual field defect only on the right eye), paresis of the right oculomotor and abducent nerve and panhypopituitarism. The hormone profile was characteristic for panhypopituitarism. The levels of blood glucose and serum electrolytes were still within the normal range. The fluid balance was not affected. The patient has received hormone



**Fig. 1 – The first patient before surgery. MRI reveals a tumour of the pituitary gland (histologically metastasis of renal cell carcinoma), destructing the surrounding bone and invading to the right parasellar space (arrow).**



**Fig. 2 – MRI of the head after the surgery with postoperative changes and without residual tumour.**

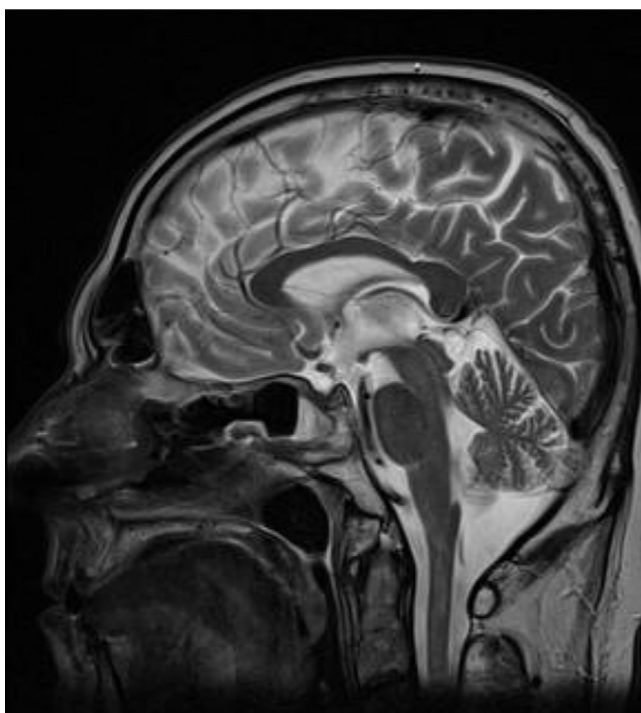
replacement therapy and as a result of progressive deterioration of vision, a decompressive operation was indicated. Through a transnasal endoscopic approach, the tumour was extensively reduced. Histology confirmed the metastasis of renal clear-cell carcinoma. Postoperatively, the visual acuity improved bilaterally, while the paresis of ocular nerves and panhypopituitarism persisted. The pain in the eyes as well as the excessive lacrimation gradually subsided. After the operation and recovery, radio- and chemotherapy followed. On the control imaging of the head after surgery, there was no tumour residue visible (Fig. 2). The same clinical status persisted also three months after surgery during the follow-up, when no signs of relapse in the pituitary were documented. The survival time of the patient was eight months.

### 2.2. The second patient

One month before the admission, a 60-year-old man started to experience fatigue, weight loss, night sweats, pain in the mid abdomen and below the right costal arch, often followed by nausea, vomiting and dizziness. A CT scan of the abdomen showed a lesion in the adrenal glands. Extended diagnostics revealed cystic lesions in the liver, calcified oesophageal lymph nodes and leukopenia. A CT-guided puncture of the right adrenal gland was performed and the histological examination confirmed a diffuse large B-cell lymphoma. Laboratory tests pointed to the hypopituitarism with impaired function of the adrenal, thyroid and gonad axis. Magnetic resonance imaging (MRI) of the head showed a tumour of the pituitary gland, spreading to the suprasellar space and compressing the optic chiasm (Fig. 3). The neurological status, including vision, was normal. Through a transnasal endoscopic approach, a biopsy of the intrasellar tumour was done. The postoperative course was good. Histology confirmed a



**Fig. 3 – MRI of the second patient before surgery showing a pituitary tumour (histologically B-cell lymphoma) spreading suprasellarly and compressing on the optic chiasm (arrow).**

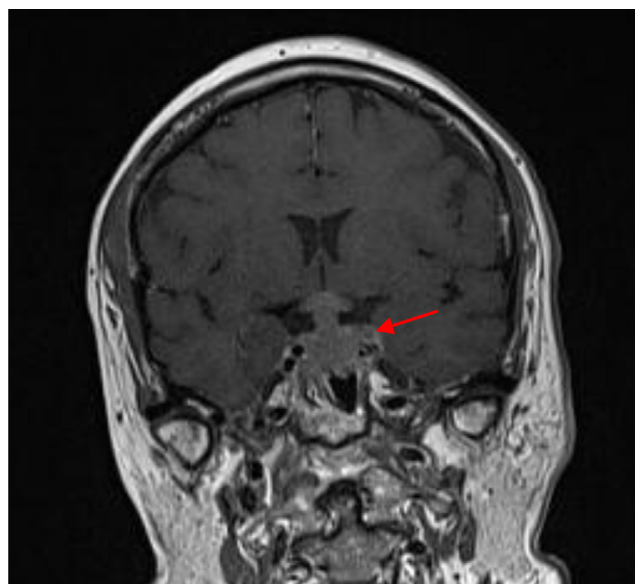


**Fig. 4 – MRI after the procedure shows the reduction of tumour (regression of the lymphoma in the central nervous system).**

diffuse large B-cell lymphoma. The oncological therapy followed. A control MRI of the head two months and then three years after surgery showed a tumour reduction and a regression of lymphoma in the central nervous system (Fig. 4). Four years after the diagnosis, the disease is still in remission. Due to panhypopituitarism, the patient needs hormone replacement therapy with hydrocortisone, thyroxin and testosterone and due to diabetes insipidus treatment with desmopressin is necessary.

### 2.3. The third patient

A 57-year-old lady was treated for breast carcinoma with metastases in the bones and lungs. She had been diagnosed with panhypopituitarism six months before the admission. The MRI of the head showed a small tumour in the pituitary gland and follow-up was recommended. Initially, the patient experienced headaches, followed by double vision when looking down due to the paresis of the right trochlear nerve and somewhat less also of the left one. A control MRI showed an increase of the tumour size with extension to the suprasellar space and towards both cavernous sinuses (Fig. 5). In few months, the tumour had grown rapidly. The vision deteriorated, as well as the bulbomotors. Through a transnasal endoscopic approach, a tumour reduction in the sellar and suprasellar space was carried out. The postoperative course after endoscopic tumour reduction in the sellar and suprasellar space was uneventful. However, cerebrospinal fluid (CSF) leakage was seen after a few days and required a revision. In addition to the nasal septum vascularized flap (Hadad flap) that was used during the initial skull base closure, focal fat grafts and collagen sponge were fitted into the osseous cranial base gaps, covering them completely. The fibrin glue was sprayed on top, sealing the defect watertightly.



**Fig. 5 – The third patient before surgery. MRI shows a pituitary tumour (histologically metastasis of breast carcinoma), which expands suprasellarly and into the cavernous sine (arrow).**

Additionally, the lumbar drainage was placed for a week, relieving the CSF pressure. The leakage stopped and the postoperative course was without incidents. The histological examination confirmed metastasis of a glandular breast carcinoma, positive for hormone receptors. Oncological treatment, which included radio- and chemotherapy, followed two weeks after the revision surgery. One year after the surgery, the patient is still being followed-up and the disease course is stable.

### 3. Discussion

Pituitary metastases are rare and can be found in 1% of resected hypophyseal tumours [1]. Among intracranial metastases, they represent from 0.8% to 1.9% of all cancer biopsies [2]. According to some studies, the incidence is between 0.14% and 28% and is increasing in recent decades due to better diagnosis and treatment of the underlying disease and prolonged survival rate of these patients [2,3]. There are not many reports about metastatic cancers into hypophysis; generally, only descriptions of individual cases and small series of patients with pituitary metastases may be found. Taking into account the biopsies involving the pituitary gland and the surrounding area of the sella, the percentage of metastases in this area increases up to 27% [1]. The most common metastatic tumours to the pituitary are breast and lung cancer in 37.2% and 24.2%, respectively [2]. In female population, the most common is breast cancer in 66% and lung cancer in 13.2%. In male population, the lung cancer predominates with 62.9%, followed in 8.6% by prostatic cancer [5,6]. At least in part the reason is that these two types of malignancies are most commonly encountered in clinical practice. Less often described are metastasis of renal cell carcinoma, gastrointestinal tumours, lymphomas, leukemias, thyroid carcinomas, myeloma, hepatocellular carcinoma and rhabdomyosarcoma (Table 1) [1,2,7-19]. When confirming the metastasis in the pituitary, there are frequently metastases present at several other locations, most often in bones.

Our patients had various types of metastases to the pituitary. The breast cancer is a common one, whereas renal carcinoma and diffuse large B-cell lymphoma are more rarely encountered. Especially sellar lymphoma is exceedingly rare. It includes primary and secondary pituitary lymphoma. Both may be accompanied by acquired immunodeficiency syndromes, whereas the later is a systemic lymphoma involving

also the pituitary gland. The mean age of the patients is almost the same, about 60-70 years of age. Since the pituitary gland has a large reserve capacity, pituitary involvement in lymphoma also appears to be asymptomatic in most cases until the advancing stage of the disease. As with metastases, the diabetes insipidus and visual disturbances are the most common clinical presentations. Histologically, B-cell non-Hodgkin lymphomas represent the majority of pituitary lymphomas. Chemotherapy is the treatment option [20-22].

The incidence of pituitary metastases is independent of gender. They are more commonly encountered in the sixth and seventh decades of life [3]. The incidence of metastasis of breast cancer in the pituitary is rising and these are described in the 6-29% of patients suffering from breast cancer. There is no clear explanation and it is assumed that the hormonal environment of the pituitary gland provides fertile soil for the implantation of metastatic cells and offers an optimal environment for their growth [1]. Especially the prolactin chemotactically affects the breast cancer cells [1,7].

The tumours may metastasize into the pituitary gland and surrounding area by several ways: (I) hematogenously into the posterior lobe, (II) from the hypothalamus or infundibulum via the portal circulation, (III) with progression of metastasis from extrasellar space and skull base, (IV) thorough meningeal spreading over suprasellar cistern into the pituitary capsule [3,7].

Most pituitary metastases are present in the posterior lobe of the pituitary. Teears et al. have analyzed 88 cases of metastatic pituitary tumours [6]. In 57%, only the posterior lobe of the pituitary gland was affected, in 13% the anterior lobe and in 12% both lobes were affected. The remainder is accounted for the location of the metastasis in the capsule or the pituitary stalk. In the posterior part, the metastases were predominant and in the anterior lobe, the necrosis prevailed. The authors suggest that the tumour of the posterior lobe of the pituitary caused an infarction of the anterior lobe, hence the necrotic tissue on histological examination. This also results in endocrine abnormalities [6].

It is assumed that most metastases are present in the posterior pituitary lobe due to its direct arterial blood supply and therefore higher likelihood of metastasis in comparison to the anterior lobe, which gets its blood supply from the hypothalamic-pituitary portal system [1,2,6]. A higher percentage of metastases in the posterior lobe can also be a result of increased contact with the dura that covers the pituitary gland and produces functional periosteum of the underlying sella [3,6]. Interestingly, there are no reports about growth of metastasis into the pituitary from the surrounding cranial bone [6]. In contrast to Teears et al., some studies found more frequent involvement of the anterior pituitary, mainly due to breast cancer metastases [1]. Because of the hormonal attractiveness, the metastatic breast cancer cells showed a higher affinity to adenohypophysis. In this research series of breast cancer metastasis, the anterior pituitary was involved in 70-82% [1].

The clinical picture of the pituitary metastasis may be unspecific. They are frequently silent. Morita et al. observed that the time from the occurrence of symptoms to the diagnosis ranges from ten days to three years, with an average of three months [7]. In our three patients, the time from the

**Table 1 – The most frequent primary sites of pituitary metastases.**

Primary site	Incidence of metastasis
Breast	37.2%
Lung	24.2%
Prostate	8.6%
Renal cell carcinoma	7.5%
Gastrointestinal tumours	6.4%
Thyroid	5.8%
Hepatocellular carcinoma	3%
Lymphomas and leukaemia	0.5%
Rhabdomyosarcoma	0.3%

onset of symptoms to the surgical treatment and confirmation of the disease ranged from three to four weeks, which confirms that metastasis to the pituitary gland may be clinically silent for a long time and become clinically manifest only when they disturbed the function of the pituitary or in case the tumour has already affected the surrounding structures. Teears et al. found that only 7% of metastases to the pituitary were symptomatic and most of them were discovered during autopsies [6]. The most common symptoms were diabetes insipidus in 32.7%, followed by ophthalmoplegia, headache, vision disturbance, which is reflected most often as bitemporal hemianopsia, impairment of visual acuity and malfunctioning of the anterior pituitary lobe [2,3,5,7]. As metastases are more frequent in the posterior pituitary lobe, the majority of patients usually first present with signs of diabetes insipidus, which may be transient and it occurs as a result of disability of infundibulum and hypothalamus [3]. The diabetes insipidus is more frequently described in the pituitary gland metastases (60%) as in pituitary adenomas (1%). Among the newly diagnosed patients with diabetes insipidus, 14–20% already had metastases in bones, which indicates advanced disease and a long-lasting quiet clinical course [1]. Similar symptoms were observed also in our patients.

With the pituitary metastases, diabetes insipidus and/or oculomotor nerve paresis are more common. On the other hand, for pituitary adenomas, the vision loss and the malfunction of the anterior lobe are more typical [2,3]. Thus, the metastases in the pituitary established paresis of eye movements in 42%, with pituitary adenomas only in 5% [5]. Invasive tumours cause visual deficits due to suprasellar growth and due to invasion into the cavernous sinus, the painful ophthalmoplegia may ensue [1]. A lot of dysfunctions of the pituitary gland may remain blurred due to progression of the underlying disease. In 56–64% of patients with symptoms of a tumour in the pituitary gland, this may be the first sign of malignancy. On the other hand, pituitary metastasis are in 20–30% the first sign of primary tumour of an unknown origin [2,7]. Hyperprolactinemia may be caused as a result of pressure on the pituitary stalk and occurs in 6.3% of cases [3]. The combination of diabetes insipidus, cranial nerve palsies (ophthalmoplegia), the rapid course of the disease, headache and age over 50 years indicate a high probability of pituitary metastasis [2–4].

For the diagnosis, the MRI of the head is necessary. The sensitive and specific criteria, which would distinguish metastasis from the pituitary adenoma, cannot be exactly set [5]. In comparison to pituitary adenomas, the pituitary metastases are characterized by erosion of the cranial bone without increasing of the sella, bell-shaped sella due to the expansion through the diaphragm, faster growth and bleeding [2,5]. The clinical picture is particularly important. However, the radiological characteristics of metastases on MRI are numerous: (I) thickening and amplification of the pituitary stalk, (II) loss of the high-intensity signal from the posterior pituitary lobe, (III) isointensity on T1- and T2-weighted images, (IV) invasion of the cavernous sinus and suprasellar spreading, (V) sclerosis in the surroundings of the sella and (VI) homogeneous appearance of the lesion [1,7]. In endocrinological examination, the endocrine dysfunction of the posterior lobe may be found, as well as anterior lobe dysfunction, which

is reflected by lower values of thyroxine, cortisol and testosterone and a higher value of prolactine. The diagnosis is definitely confirmed by pathohistological examination. The differential diagnosis may include craniopharyngeoma, germinoma, histiocytosis X and pituitary adenoma [7].

The treatment for metastases to the pituitary includes surgery, stereotactic radiosurgery, radiotherapy with target irradiation of the whole head, chemotherapy and hormone replacement therapy. In case of surgical treatment, the resection through the endoscopic transsphenoidal approach is performed in most cases. In case of larger lesions, which spread suprasellary and to the cavernous sinus, it is possible to use a transcranial approach. A complete resection of the tumour is usually difficult because of good vascularization and consequently increased bleeding, local ingrowth into the surrounding bone and the cavernous sinus and into the hypothalamus and optic nerves [3]. The surgical resection, regardless of how radical is performed, does not affect the survival of these patients [2]. It usually only leads to the improvement of symptoms such as visual acuity, pain, ophthalmoplegia, thus enabling a better quality of life when a good resection is combined with additional radiotherapy [2,7]. Malfunctions of the anterior pituitary lobe and double vision due to the cranial nerve palsies are usually permanent. Improved survival has been demonstrated in local control of tumour with adjuvant radiotherapy or chemotherapy [1,3,7]. Another reasonable option for treatment of pituitary tumours besides microsurgery is also stereotactic radiosurgery, which offers both safe and effective treatment for various intracranial pathologies. Although not curative in malignant tumours, it has been effective as a palliative approach for most patients, improving their survival and the quality of life. On the other hand, radiosurgery in benign tumours leads to the control of tumour size in the majority of patients [23,24].

The indications for surgical treatment are the mass effect of the tumour with deterioration of vision, pain and the need to obtain histological sample [3,7]. Morita et al. reported a study of 36 patients with pituitary metastases. They operated on 21 patients. Surgery was performed in 16 patients over a transsphenoidal approach and in five patients a transcranial route was used because the tumour was larger and extended suprasellary and into the cavernous sinus. Described among the complications of transsphenoid intervention were cerebrospinal fluid leak, carcinomatous meningitis and deterioration of endocrine function [7].

The surgical treatment is usually followed by adjuvant radiotherapy, with the possibility of local irradiation or irradiation of the whole head. Chemotherapy is also widely used, however; its effect in the studies so far is not clearly defined [1]. A palliative therapy is recommended by some authors [7].

The prognosis of the disease depends on the type of the tumour or the degree of malignancy of the primary tumour. The metastases to the pituitary gland are usually discovered in the terminal phase of the disease, when disseminated metastases are usually present. Due to concomitant symptoms of malignancy, such as weakness, vomiting and weight loss, the symptoms of pituitary metastases are often obscured [3,6,7]. Micrometastases may also be present and they are not often evident on diagnostic imaging. In these cases, the

prognosis is poor. Irrespective of the type of therapy, the median overall survival is from six to 22 months and only 10% of patients survive more than one year [1,4,7]. Death usually occurs due to the advancement of metastases, other brain metastases, pulmonary embolism, mass effects of the metastasis in the pituitary gland, meningeal carcinomatosis and local growth of the primary tumour [7].

#### 4. Conclusions

Although the metastases to the pituitary are rare, their incidence is rising with the advancement of medical diagnostics and the prolongation of the survival of the cancer patients. In case of diabetes insipidus, elderly patient, rapid progression of relevant symptoms and lesions in the area of the pituitary gland visible on MRI of the head, it is necessary to think about pituitary metastasis. Although a successful operative and adjuvant therapy may help to improve the symptoms and quality of life, the long-term survival of these patients depends on the success in the treatment of the underlying disease.

#### Conflict of interest

None declared.

#### Acknowledgement and financial support

None declared.

#### Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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