Clear cell neuroendocrine tumor of the pancreas in von Hippel–Lindau disease: a case report and literature review

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Submitted: 2016-12-21   Accepted: 2017-03-02   Published online: 2017-05-15

Key words: neuroendocrine tumors; pancreas; von Hippel-Lindau disease; carcinoma; renal cell; multiple endocrine neoplasia type 1

Abstract
Clear cell neuroendocrine tumor (NET) of the pancreas is found in von Hippel–Lindau (VHL) disease, multiple endocrine neoplasia type I (MEN I), and sporadic form. Clear cell NETs are often misdiagnosed as metastatic renal cell carcinoma. A 47-year-old woman with VHL was found to have a mass in the pancreatic tail and two masses in the right kidney with two cysts. A distal pancreatectomy and right radical nephrectomy were performed. The pancreatic lesion was a well-circumscribed, golden-yellow solid mass, which was lobulated by septal fibrosis. Microscopically, the tumor consisted of entirely of clear cells with prominent nucleoli. The tumor cell nests were separated by collagen fibrosis. Immunohistochemical studies were positive for the neuroendocrine markers and vimentin. Synchronous kidney tumors were clear cell renal cell carcinoma and cystic renal cell carcinoma. Those with syndrome are younger than those without syndrome. Sporadic tumors have larger size and higher grade than those of VHL and MEN I. Stromal sclerosis is frequently observed in VHL, compared with the other two groups. In the absence of a documented genetic profile and family history, awareness of these features should help us to diagnose clear cell pancreatic NETs resembling metastatic renal cell carcinoma.

INTRODUCTION
Neuroendocrine tumors (NETs) of the pancreas comprise 1% to 2% of all pancreatic neoplasia (Bosman et al. 2010). Microscopically, they are typically composed of uniform, cuboidal cells with eosinophilic to amphophilic cytoplasm and coarsely clumped chromatin-nuclei, referred to as “salt and pepper” chromatin, and may be arranged into trabeculae, festoons, or solid nests (Chetty & Asa 2004). Occasionally, however, clear cells or vacuolated lipid-rich cells may be identified (Guarda et al. 1983). Clear cell NET of the pancreas is regarded as a distinct neoplasm of von Hippel–
Lindau (VHL) disease (Chetty et al. 2004; Hoang et al. 2001; Kakkar et al. 2016; Lubensky et al. 1998). Pancreatic NETs are seen in 10% to 15% of VHL and 60% of the tumors have a focal or prominent clear cell component. In multiple endocrine neoplasia type I (MEN I), the incidence of clear cell pancreatic NET is 37.5% (Fryer et al. 2012). Sporadic pancreatic NETs with clear cytoplasm have rarely been described in patients not having either syndrome (Ayub & Dodge 2010; Nunobe et al. 2003; Ordóñez & Silva 1997; Singh et al. 2006).

When patients have concurrent clear cell renal cell carcinoma or a history of clear cell renal cell carcinoma, clear cell NETs composed exclusively of clear cells are often misdiagnosed as metastatic renal cell carcinoma (Hoang et al. 2001; Singh et al. 2006).

This report presents a case of clear cell NET of the pancreas showing dual expression with epithelial and mesenchymal differentiation in a VHL patient with clear cell renal cell carcinoma. We also review the clinicopathological characteristics of pancreatic NETs with clear cell changes.

CASE REPORT

Case

A 47-year-old woman was found to have an enhancing mass measuring 2.4×1.8 cm in the pancreatic tail with many pancreatic cysts and two enhancing masses measuring 1.3 cm and 1.2 cm in the right kidney with two cysts on computed tomography. The pancreatic mass had been discovered 3 years previously in a state of focal enhancement and had grown over the last few months. The differential diagnosis included a NET and other pancreatic cancers. No remarkable findings were observed in other organs. There were no symptoms or signs of systemic disease, and the results of laboratory tests were unremarkable. Mutation analysis of her VHL gene identified a missense mutation (p.Pro86Arg). Four years earlier, she had undergone a partial nephrectomy for clear cell renal cell carcinoma of the left kidney. Both her mother and her brother had VHL. A distal pancreatectomy and right radical nephrectomy were performed. She had no postoperative complications.

Pathological findings

Grossly, the pancreatic lesion was a well-circumscribed, golden-yellow solid mass, which was lobulated by septal fibrosis. Multilocular cysts, filled with serous fluid, were identified adjacent to the solid mass (Figure 1). Microscopically, the tumor consisted of solid nests within a delicate vascular network of uniform cuboidal cells with prominent nucleoli. Individual cells throughout the lesion were characterized by foamy and clear vacuolated cytoplasm (Figure 2A). Periodic acid Schiff (PAS) stain failed to demonstrate the presence of glycogen in the cytoplasm. The tumor cell nests were separated by collagen fibrosis (Figure 2B). The mitotic was less than 2 per 10 high-power fields and the Ki-67 index was 2%. Immunohistochemical studies were positive for the neuroendocrine markers, synaptophysin, chromogranin-A, and CD56 (Figure 2C). In addition, the tumor showed dual expression with epithelial and mesenchymal differentiation, confirmed by strong reactivity for cytokeratin and vimentin (Figure 2D). The cystic lesions of the pancreas were of variable size and lined by a single layer of cuboidal cells with pale eosinophilic to clear cytoplasm, which stained with PAS. These microcystic serous cystadenomas did not express neuroendocrine markers.

The patient had synchronous renal cell carcinoma. The two masses in the right kidney were grade 2 clear cell renal cell carcinoma and cystic renal cell carcinoma, and were negative for neuroendocrine markers, but positive for vimentin and CD10.

![Fig. 1.](image1.png) Macroscopically, the well-circumscribed mass in the pancreatic tail was golden-yellow and solid with septal fibrosis, and was accompanied by multilocular cysts.

![Fig. 2.](image2.png) Microscopically, the uniform cuboidal cells with prominent nucleoli within a delicate vascular network showed a solid nest growth pattern. Individual cells were characterized by foamy and clear vacuolated cytoplasm (A). The tumor cell nests were separated by collagen fibrosis (B). Immunohistochemical studies were positive for synaptophysin (C) and vimentin (D).
DISCUSSION

Here, we described a case of solitary clear cell pancreatic NET in VHL with synchronous clear cell renal cell carcinoma. The pancreatic tumor consisted entirely of clear cells with prominent nucleoli, unlike the reported clear cell pancreatic NET of VHL, which had typical features reminiscent of NET in some areas (Bosman et al. 2010; Chetty & Asa 2004; Chetty et al. 2004; Hoang et al. 2001; Kakkar et al. 2016; Lubensky et al. 1998; Singh et al. 2006). In addition, this tumor expressed vimentin. One study described that 2 of 11 clear cell pancreatic NET of VHL, which had typical features reminiscent of NET in some areas (Bosman et al. 2010; Chetty & Asa 2004; Chetty et al. 2004; Hoang et al. 2001; Kakkar et al. 2016; Lubensky et al. 1998; Singh et al. 2006). In addition, this tumor expressed vimentin. One study described that 2 of 11 clear cell pancreatic NET of VHL, which had typical features reminiscent of NET in some areas (Bosman et al. 2010; Chetty & Asa 2004; Chetty et al. 2004; Hoang et al. 2001; Kakkar et al. 2016; Lubensky et al. 1998; Singh et al. 2006). In addition, this tumor expressed vimentin. One study described that 2 of 11 clear cell pancreatic NET of VHL, which had typical features reminiscent of NET in some areas (Bosman et al. 2010; Chetty & Asa 2004; Chetty et al. 2004; Hoang et al. 2001; Kakkar et al. 2016; Lubensky et al. 1998; Singh et al. 2006). In addition, this tumor expressed vimentin. One study described that 2 of 11 clear cell pancreatic NET of VHL, which had typical features reminiscent of NET in some areas (Bosman et al. 2010; Chetty & Asa 2004; Chetty et al. 2004; Hoang et al. 2001; Kakkar et al. 2016; Lubensky et al. 1998; Singh et al. 2006). In addition, this tumor expressed vimentin. One study described that 2 of 11 clear cell pancreatic NET of VHL, which had typical features reminiscent of NET in some areas (Bosman et al. 2010; Chetty & Asa 2004; Chetty et al. 2004; Hoang et al. 2001; Kakkar et al. 2016; Lubensky et al. 1998; Singh et al. 2006). In addition, this tumor expressed vimentin. One study described that 2 of 11 clear cell pancreatic NET of VHL, which had typical features reminiscent of NET in some areas (Bosman et al. 2010; Chetty & Asa 2004; Chetty et al. 2004; Hoang et al. 2001; Kakkar et al. 2016; Lubensky et al. 1998; Singh et al. 2006). In addition, this tumor expressed vimentin. One study described that 2 of 11 clear cell pancreatic NET of VHL, which had typical features reminiscent of NET in some areas (Bosman et al. 2010; Chetty & Asa 2004; Chetty et al. 2004; Hoang et al. 2001; Kakkar et al. 2016; Lubensky et al. 1998; Singh et al. 2006). In addition, this tumor expressed vimentin. One study described that 2 of 11 clear cell pancreatic NET of VHL, which had typical features reminiscent of NET in some areas (Bosman et al. 2010; Chetty & Asa 2004; Chetty et al. 2004; Hoang et al. 2001; Kakkar et al. 2016; Lubensky et al. 1998; Singh et al. 2006). In addition, this tumor expressed vimentin. One study described that 2 of 11 clear cell pancreatic NET of VHL, which had typical features reminiscent of NET in some areas (Bosman et al. 2010; Chetty & Asa 2004; Chetty et al. 2004; Hoang et al. 2001; Kakkar et al. 2016; Lubensky et al. 1998; Singh et al. 2006). In addition, this tumor expressed vimentin. One study described that 2 of 11 clear cell pancreatic NET of VHL, which had typical features reminiscent of NET in some areas (Bosman et al. 2010; Chetty & Asa 2004; Chetty et al. 2004; Hoang et al. 2001; Kakkar et al. 2016; Lubensky et al. 1998; Singh et al. 2006). In addition, this tumor expressed vimentin. One study described that 2 of 11 clear cell pancreatic NET of VHL, which had typical features reminiscent of NET in some areas (Bosman et al. 2010; Chetty & Asa 2004; Chetty et al. 2004; Hoang et al. 2001; Kakkar et al. 2016; Lubensky et al. 1998; Singh et al. 2006). In addition, this tumor expressed vimentin. One study described that 2 of 11 clear cell pancreatic NET of VHL, which had typical features reminiscent of NET in some areas (Bosman et al. 2010; Chetty & Asa 2004; Chetty et al. 2004; Hoang et al. 2001; Kakkar et al. 2016; Lubensky et al. 1998; Singh et al. 2006). In addition, this tumor expressed vimentin. One study described that 2 of 11 clear cell
NETs (18.2%) were positive for vimentin and they were not associated with any other lesions or syndromes (Singh et al. 2006). These features bear a striking resemblance to clear renal cell carcinoma with prominent nucleoli and sinusoidal vasculature, in which the tumor is indistinguishable from renal cell carcinoma, without ancillary tests such as immunohistochemistry, electron microscopy, and special stains (Cenkowski et al. 2011; Hoang et al. 2001; Shah et al. 2015; Singh et al. 2006). Ultimately, our case was confirmed by immunohistochemistry for neuroendocrine markers.

We reviewed the clinicopathological characteristics of pancreatic NETs of VHL with clear cell features. Including the present case, some articles describe clear cell NETs of the pancreas including cases associated with VHL and MEN 1, and sporadic cases (Ayub & Dodge 2010; Chetty et al. 2004; Fryer et al. 2012; Guarda et al. 1983; Hoang et al. 2001; Kakkar et al. 2016; Kaur et al. 2016; Lubensky et al. 1998; Nunobe et al. 2003; Ordóñez & Silva 1997; Singh et al. 2006). As summarized in Table 1, patients with associated syndromes are younger than patients with no associated syndrome. Among clear cell NETs, sporadic tumors are larger than those of VHL and MEN 1. Sporadic tumors have a higher grade than those of VHL and MEN 1. Early detection causes the difference between sporadic cases and syndrome-associated cases when a family history or other syndrome-related lesions in VHL and MEN 1 lead to screening. The NETs in VHL are accompanied by simple cysts and serous cystadenomas, and those of MEN 1 are associated with multiple neuroendocrine lesions, while most sporadic cases have no other pancreatic lesions (Fryer et al. 2012; Hoang et al. 2001; Lubensky et al. 1998). Stromal sclerosis is frequently observed in VHL, compared with the other two groups. Metastatic renal cell carcinoma to the pancreas tends to manifest as a solitary lesion (Cheng & Chuah 2016; Ordóñez & Silva 1997; Shah et al. 2005). Our patient’s pancreatic tumor also had stromal sclerosis, while the renal cell carcinoma did not show the pathologic feature.

In summary, we describe the clinicopathological characteristics of clear cell pancreatic NETs in syndrome-associated and sporadic groups. In the absence of a documented genetic profile and family history, awareness of these features should help us to diagnose clear cell pancreatic NETs resembling metastatic renal cell carcinoma.

ACKNOWLEDGMENTS

This work was supported by the Soonchunhyang University Research Fund.

Conflict of Interest: The authors declare that they have no competing interests.

REFERENCES

Multiple sclerosis in an acupuncture practice

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Submitted: 2017-01-15 Accepted: 2017-03-01 Published online: 2017-05-15

Key words: Autoimmune Diseases; Multiple Sclerosis; Demyelinating Diseases; Fatigue; Pain; Acupuncture Therapy; Traditional Chinese Medicine

Abstract
Multiple sclerosis (MS) is a severe autoimmune demyelinating disease that affects nervous system, has high morbidity and mortality and no effective targeted therapies are available. We present a case of 66-year-old female patient who has been treated by both conventional and Chinese traditional medicine after diagnosis was confirmed in 2008 as MS and antiphospholipid syndrome associated with CNS vasculitis. After diagnosis with clinical image confirmed with CT and MRI scan, where demyelinating zones were present, she started pharmacological therapy without major improvement. Patient suffered with fatigue, walking difficulties, weakness, was unable to articulate due to vocal cords spasms. We started acupuncture treatment in 2010 with herbal supplement therapy as well and patient had in total of 197 sessions with 10 session’s cycle and 2–3 months pause. Patient's mobility was significantly improved after therapy, as well as vocal cord spasms and she gained back her articulation. Subjectively, patient also reported pain relief, mobility and fatigue improvement.

Traditional Chinese medicine showed to be effective tool for pain and spasm relieving and can be powerful complementary tool in patients with chronic diseases, such as MS.

INTRODUCTION

Multiple sclerosis is a chronic autoimmune disease characterized by inflammation, demyelination, axonal/neuronal damage, oligodendrocyte loss, and oxidative stress with myelin destruction in the spinal cord, brain and optical nerve, although severity of the disease and clinical course may vary (Bartova et al. 2016). Pathophysiological findings suggest that disease is associated with the mitochondrial DNA damage (Gvozdjakova et al. 2017) and has some epidemiological and pathological signs of infection.

Spasticity accompanying MS is consequently a result of corticospinal motor neuron damage and affects approximately 34 % of people with diagnosis. It often occurs with fatigue and pain and leads to contractures. The most frequently used Ashworth scale evaluates the resistance to passive movement (measured values are 0–5) (Rizzo et al. 2004; Cibulcik 2015). Visual Analogue Scale (VAS) or more complex Multiple Sclerosis Functional Composite (MSFC) are also used (Kantorova et al. 2012).

Multiple Sclerosis mostly affects the Western and Northern hemisphere population and the disease has a predilection for white races and for women. According to the epidemiological data,
prevalence is as high as >100/100,000 inhabitants in Europe and America, whereas in African countries is usually lower than 2/100,000 and in China less than 1/100,000 (Otero-Romero et al. 2016).

Etiology of the myelin loss remains unknown. The first symptom in young people is retrobulbar neuritis usually manifested as a blurred or distorted vision. In older patients, MS is manifested as the weakness in limbs, pain, prolonged fatigue and depression (Mohr et al. 2006; Raisi et al. 2015). Paresthesia in fingers, dizziness, vomiting or nausea, speech difficulties, memory and concentration problems, pain and colusions in legs, incoordination, nystagmus, electric-shock sensation along the spine or in limbs, numbness in limbs, urinary urgency, impotence, incontinence low vitamin D blood levels (Jahromi et al. 2016) and other symptoms may be present in patients.

Diagnosis is usually made after white matter lesion findings on MRI (Wu et al. 2002; Haiderr et al. 2016), or typical cerebrospinal fluid findings of lumbar puncture are found (Freedman et al. 2005; Kottil 2009; Sosvorova et al. 2015) with clinical correlation of above-mentioned symptoms. According to traditional Chinese medicine, in patients with MS Blood is infected by latent heat (Sun 1997; Xia et al. 2010).

Therapy for MS include immunosuppressive drugs such as azathioprine, cyclophosphamide and cyclosporine, which might have potential to slow down progression of the disease, however all of them have potentially serious adverse effects. Recently, it was shown that interferon-β-1b can be useful by diminishing the exacerbation rate in MS without leading to unacceptable adverse effects. However, symptomatic treatment still remains of crucial importance in the management of MS patients. Usually symptoms can be alleviated to some extent with pharmacological interventions, rehabilitation procedures and psychosocial consultations. Acupuncture, herbs and other non-conventional methods are less frequent (van Oosten et al. 1995; Maciocia 2007).

The prognosis depends on the type of MS, sex, age and race, accessory symptoms, mental condition and the degree of disability. The course of disease is usually easier in women and those who were diagnosed at younger age (Dolejšová 2016).

CASE

Female patient born in December 1950, treated for MS since 2008 when the diagnosis was confirmed as EDSS (Expanded Disability Status Scale) 5.5 type, antiphospholipid syndrome associated with CNS vasculitis.

According to the patient’s records, she had repeated sinus infection treated with antibiotics and several lower respiratory tract infections, including pneumonia and tuberculosis treated in sanatorium. The patient also underwent surgical procedures for spasmodic dysphonia and stridor in 1997 and 2000, but despite of symptoms, brain MRI at 48 years of age (1998) was negative. Since 2005, the spasm of vocal cords has been accompanied by aphonia and treatment by botulotoxine injections to vocal cords was terminated due to no effect.

In 2008, CT and MRI of cervical spine and brain were performed. Brain MRI found juxtacortical demyelinated lesions 8×5mm, bilateral frontoparietal (FTP), juxtacortical and paraventricular small demyelinated lesions in the white matter. The patient was diagnosed with multiple sclerosis based on gait difficulty, weakness, incoordination and MRI findings. Pharmacological treatment with Synacthen (cosyntropin), Diprophos (betametason), Solumedrol (methylprednisolon), Prednison (prednisolon), Baclofen (baclofen), Pyrabene (piracetam), Cavinton (vinpocetine), was administered without positive effect. Other diagnoses found in records were: pancreatopathy, chronic peptic ulcer and Hashimoto’s Struma. Follow-up brain MRI in 2013 confirmed diagnosis, but didn’t show any new lesions.

Patient came to our practice for the first time in December 2010. Communication was performed in writing due to aphonia. Her major complains were severe pain, numbness insomnia, weakness and loss of voice.

After the primary examination, which showed significant Qi deficiency and consequently empty Heat, Dampness and Blood stagnation, we have started an acupuncture treatment. Acupuncture sessions took place once a week for the period of 10 weeks. In the first stage we used mainly Hua-tuo-jiaji points from C5 to S2 vertebrae. 5–7 cm long needles were applied to every other vertebra. The treatment was supplemented by Chinese herbs, Ba Zhen Wan formula and later by combination of Bu Zhong Yi Qi Wan and Gui Pi Wan formula. After 10 acupuncture sessions and herbal therapy her walking difficulties and tingling in fingers improved significantly and she was able to walk with better stability.

We applied also other points combinations in particular stages of treatment to balance Yin and Yang, replenish Qi and alleviate empty Fire by strengthening Yi: Sanyinjiao (Sp6), Taixi (K3), Zhaobai (K6), Zusanli (St36), Fenglong (St40) points etc. We have often used the points on the Chong Mai extraordinary channel, Gongsun (Sp4) in combination with Neiuan (C56) to replenish Yuan Qi and improve the overall internal organ microcirculation.

The patient subjectively indicated improvement in pain relief, mobility and weakness improvement.

However, severe vocal cords spasms persisted at any attempts to speak, so we were dealing with the vocal cords disorder as well. The following recommended acupoints were used for the vocal cords treatment: Lianquan (CV 23), Huagai (CV20), Tongli (H15), Zhaobai (K6), Lidui (St45), Neiting (St44), Renying (St9), Hegu (LI4), Taichong (Liv3). Acupuncture was supplemented with minimum doses of the Tian Ma Gou Teng Wan...
formula which relieves the spasms and improves the blood circulation in the brain. After two year therapy, patient was first time able to speak about her problems with mild pain in vocal cords. Unfortunately, relapse of the vocal cords spasm occurred after 3 months and she has lost her voice again. The treatment by acupuncture continued, the patient regained her voice in February 2014 and she has been able to communicate since then with minor occasional impairment but without the loss of articulation.

In total she has attended 197 acupuncture sessions in cycles of 10 sessions followed by 2–3 months pause. Besides the mobility improvement and pain relief, the renewed ability to speak was the most significant outcome of the treatment from the subjective point of view.

DISCUSSION

Approximately 85% of patients with multiple sclerosis indicate impaired mobility as one of the major limitations in their daily life. Acupuncture studies found a reduction of spasticity and improvement of fatigue and imbalance in patients with multiple sclerosis (Hopwood & Donnellan 2010). Recent Portugal study also shows significant effect of acupuncture on gait in patients with MS (Criado et al. 2017).


However, the majority of the studies in this area are poorly designed, often without control, randomization, or blinding. Although many of the studies suggest that acupuncture is successful in improving MS related symptoms, lack of statistical rigor and poor study design make it difficult to draw any conclusions about the true effectiveness of this intervention in the MS population (Karpatin et al. 2014). More well designed studies are therefore needed on bigger cohorts, for confirming these hypotheses.

Low prevalence of MS in Asia generally and China in particular (around 0.8/100,000) caused lack of data from traditional sources. In Chinese medicine, MS has been described as a „modern disease”, in 1974. Also the definition and pathology of MS is formulated in different terms and based on different concepts than worldwide, which is partly the reason why the concept of the TCM treatment and its classification in databases of large clinical trials are of little use.

CONCLUSION

The absolute number of individuals with MS is increasing in the western countries and represents a substantial challenge to treatment, prevention, health promotion, and rehabilitation. Patients with MS face many challenges in their everyday life and their quality of life is often deteriorated. Since there is no curative treatment for MS, more studies for alternative treatment including TCM are needed. (Zeng et al. 2013) There is a lack of significant data in this area and more studies for alternative treatment with good design would be beneficial for patients and their quality of life. We believe, that example of our case showed, that acupuncture with supplementary therapy with traditional Chinese medicine can be effective treatment of some symptoms accompanying patients with MS.

REFERENCES


16 Krupp L (2012). Fatigue in intrinsic to multiple sclerosis (MS) and is the most commonly reported symptom of the disease. Mult Scler 12: 204–208.


