Cervical neuroendocrine tumor in a young female with Lynch Syndrome

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C A S E   R E P O R T

Abstract

Neuroendocrine tumors rarely occur in the cervix or other components of the reproductive system. These tumors have been associated with microsatellite instability, are very aggressive and often associated with poor outcome. Lynch syndrome is an inherited cancer syndrome that has also been associated with microsatellite instability. Here we report a 34-year-old female with Lynch syndrome and a family history of loss of DNA mismatch of the hereditary non-polyposis colorectal cancer repair gene expression who presented with a neuroendocrine tumor of her cervix as the first manifestation of Lynch syndrome. This is the first case reported of a neuroendocrine tumor of the cervix in a patient with Lynch syndrome. We also review the relationship between Lynch Syndrome and neuroendocrine tumors.

Abbreviations:
HPV	- human papillomavirus
MLH1	- mutL homologue 1
MMR	- mismatch repair
MSH2	- MutS protein homolog 2
MSI	- microsatellite instability
NET	- Neuroendocrine tumors
PAP	- Papanicolaou

INTRODUCTION

Neuroendocrine tumors (NET) are neoplastic lesions that arise from the secretory cells of the neuroendocrine system; they can occur in the gastrointestinal tract, pancreas, lungs and other organs including the reproductive system (Kloppel *et al.* 2004; Plöckinger *et al.* 2004). NETs have a classification spectrum that includes well-differen-tiated carcinoma and poorly differentiated tumors, the latter including small cell and large cell carcinoma (Bosman, 2010). While diffusely distributed in various tissues, NETs have rarely been reported in the uterine cervix, accounting for no more than 2% of cervical tumors (Albores-Saavedra *et al.* 1997). NETs of the cervix manifest clinical and biological findings different than those found in squamous endocervical carcinoma, making it a unique entity compared to other NETs (Bifulco *et al.* 2009).

An association between NETs of the cervix and human papilloma virus 16 and 18 has been reported (Ambros *et al.* 1991). These relatively rare NETs arise from neuroendocrine cells that occur normally in the endocervix, but undergo neuroen-docrine metaplasia and hyperplasia (Savargaonkar

et al. 1996). These cervical NET are specifically classified into large cell NET, small cell NET, typical carcinoid cells, and atypical carcinoid cells (Mannion *et al.* 1998). Small cell NETs typically have a very aggressive clinical course and a poor outcome (Albores-Saavedra *et al.* 1997; Conner *et al.* 2002). These tumors can be identified pathologically by immunostaining with antibodies directed to neuroendocrine molecules such as synaptophysin (Gardner *et al.* 2011).

Lynch syndrome is an inherited cancer syndrome associated with microsatellite instability (MSI) that results in an increased early manifestation of tumors most commonly in the colon, endometrium, ureters, ovaries, as well as other organs (American Gastroenterological Assocation 2001). It is a familial disease that should be suspected in individuals who develop cancer at a relatively young age and those with multiple relatives with cancer (Vasen *et al.* 1991; 1999). Lynch syndrome is caused by the loss one of many DNA mismatch repair (MMR) proteins including mutL homologue (MLH)1and others (American Gastroenterological Assocation 2001; Boland *et al.* 1998).

We report the novel case of a young woman with known Lynch syndrome in which a NET occurred in the cervix with lethal results and discuss the case in the context of the extant literature.

CASE PRESENTATION

The patient in this report was a 34-year-old white female recently diagnosed with Lynch syndrome associated with a MLH1 protein expression defect. The relevant family history included her brother who died of metastatic colon cancer at age of thirty-one, and a second brother recently diagnosed with colon cancer. This striking medical history prompted the family to be screened for Lynch syndrome. The patient in this case and all of her siblings manifested the presence of the disease characterized by loss of MLH1 MMR protein expression.

While waiting to be screened for colon cancer with a colonoscopy, she presented to our hospital with abdominal pain and irregular menses. The pain was associated with dysuria and with vaginal bleeding. On examination, her vital signs were stable. The rest of the physical examination was unremarkable except for mild lower abdominal tenderness. In the pelvic examination, an eight centimeter mass was palpated. It was firm and immobile as it was fixed to the lower uterine segment. It extended bilaterally to the walls of vagina. The cervix was dilated and filled with the mass.

Laboratory results included a normal hematology and biochemistry panels excluding anemia, renal failure or liver disease. Abdominal and transvaginal ultrasounds showed multiple abnormalities including an enlarged uterus measuring 11.4 cm × 7.6 cm × 6.3 cm with an abnormal cavity showing areas of increased echogenicity especially in the fundus. The cervix was irregular in appearance with an underlying cervical mass of unclear margins and with additional areas of atypical echo texture suggestive of enlarged lymph nodes in the lower pelvis. Magnetic resonance imaging showed a focal mass in the posterior cervix and lower uterine segment, and an irregular endometrium and significantly enlarged para-aortic and iliac lymph nodes.

A biopsy of the cervical mass was done. While the results were pending, the patient was discharged only to return a week later with marked increase in her abdominal pain and vomiting. In addition, she noted rapid onset of abdominal distention. The patient was now quite anemic with a respiratory rate of 24 breaths/minute and a heart rate of 129 beats/minute and orthostatic hypotension. Abdominal distension with ascites was present. In contrast to previous generally normal laboratory findings, serum sodium was 116 mmol/L, creatinine was 7.6 mg/dL, potassium was 6.3 mmol/L, and bicarbonate was 14 mmol/L. A thyroid stimulating hormone level and a cosyntropin stimulation test were normal.

Histologic sections of the cervical tumor showed invasion of the stroma with a population of small round cells (Figure 1A). The individual cells had scant cytoplasm (Figure 1B). No evidence of mucin production or squamous differentiation was present. The nuclei demonstrate a bimorphic appearance with some nuclei being pyknotic and markedly hyperchromatic. Other nuclei had a paler chromatin appearance with distinct nucleoli (Figure 1C). Because the differential diagnosis included lymphoma and poorly differential neuroendocrine carcinoma, immunohistochemistry for common leukocyte antigen, chromogranin and synoptophysin was performed. The neoplastic cell population demonstrates strong cytoplasmic staining for synaptophysin in some cells (Figure 1D). Common leukocyte antigen and chromogranin were negative. Based on the cell morphology and immunohistochemical findings, a diagnosis of small cell neuroendocrine carcinoma was made. Ascites were confirmed upon repeating the ultrasound. Drainage of the ascitic fluid showed malignant cells similar to the above biopsy, suggesting peritoneal metastasis. Renal failure necessitated dialysis. Following the request of the patient and her family, hospice care was initiated and the patient expired.

DISCUSSION

NETs are neoplastic lesions arising from the secretory cells of the neuroendocrine system and occur in the gastrointestinal tract, pancreas, lungs and other systems including the reproductive system (Kloppel *et al.* 2004; Plöckinger *et al.* 2004). The most common NETs are carcinoid or gastrointestinal tumors. They may cause symptoms related to production of various factors. NETs produce abundant growth factors, peptides, bioactive amines and hormones that may be secreted giving rise to specific syndromes; diarrhea and flushing with carcinoid tumor, Zollinger-Allison syndrome with
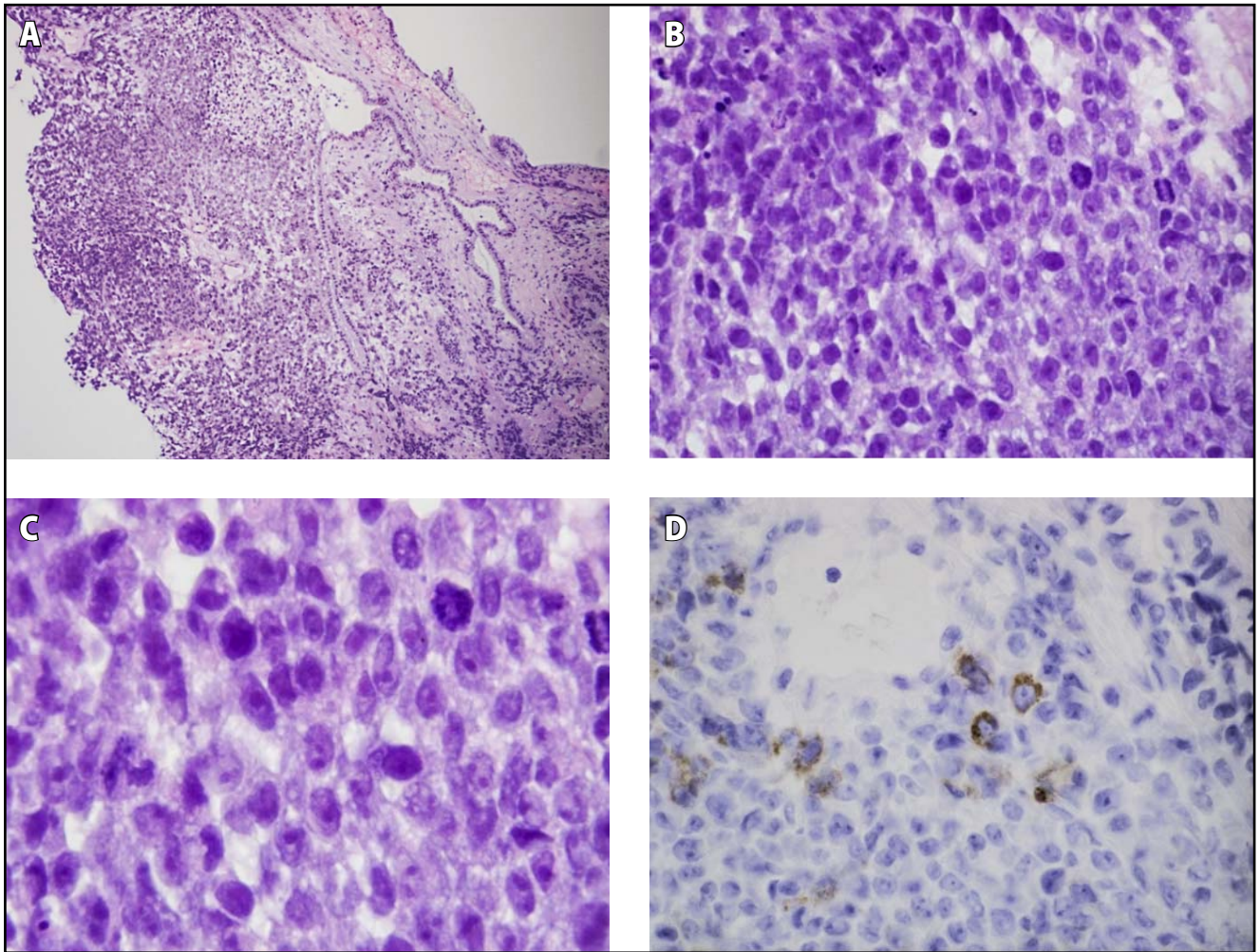
Fig. 1. (A) Section of cervix showing a proliferation of small round cells infiltrating the stoma and in glands (H+E, ×40), **(B)** Neoplastic cells characterized by scant cytoplasm surrounding hyperchromatic round to oral nuclei. There were no glandular structures or intracytoplasmic mucin. (H+E, ×400), **(C)** Small cell population with some cells having hyperchromatic or pyknotic nuclei while others have paler chromatin with prominent nucleoli (H+E, ×600), **(D)** A subpopulation of cells shows strong cytoplasmic staining with antibodies directed against synaptophysin (Immunoperoxidase, ×400).

gastrinomas, hypertension and other manifestations associated with excess catecholamine production with pheochromocytomas, Verner-Morrison syndrome with excess pancreatic vasoactive intestinal peptide production, Cushing's syndrome with excess pituitary adrenocorticotrophin production, and symptoms related to excess secretion of insulin, glucagon and other peptides (Hochwald *et al.* 2002; Klimstra *et al.* 2010).

NETs generally consist of uniform sheets of small round cells with similar nuclei. Pathologically these tumors are stained with silver staining, by which they are divided into argentafin reactive (stain uptake and silver reduction/staining) or argyrophilic (no uptake or silver staining). Immunocytochemical identification of neuroendocrine cell markers is used to confirm NETs and these tumors stain positive for chromogranin, neuron-specific enolase, and/or synaptophysin. These cells also contain electron-dense granules and small clear vesicles, which are similar to synaptic vesicles of neurons (Klimstra *et al.* 2010).

The incidence of NETs in the United States is 5.25 per 100,000 persons. NETs are divided into well-differentiated neuroendocrine carcinoma, and poorly differentiated tumors, the latter including small cell and large cell carcinoma (Bosman 2010). While diffusely distributed, NETs rarely occur in the uterine cervix, accounting for only 2% of NETs (Albores-Saavedra *et al.* 1997). The incidence rate of these NETs is 0.06 per 100,000 women between age of twenty two and eighty seven. The reported incidence is increasing due to higher ability to correctly diagnose and recognize such tumors. First described in 1957, small cell NET and large cell NET are pathologically different but both share a similar natural history and are treated in a similar fashion (Reagan *et al.* 1957).

An association exists between NET of the cervix and human papillomavirus (HPV)16 and 18 (Ambros *et al.* 1991). Two HPV oncoproteins E6 and E7 inactivate the antiapoptotic molecules p53 and Rb, respectively. E6 oncoproteins directly inactivate p53, while E7 forms a

complex with Rb leading to its inactivation. Both p53 and Rb are tumor suppressors regulating the cell cycle. Thus disruption of these proteins leads to increased risk of malignancy (Wang & Lu, 2004). These tumors arise from neuroendocrine cells that occur normally in the endocervix, but undergo neuroendocrine metaplasia and hyperplasia (Savargaonkar *et al.* 1996). Because of their epithelial origin, these tumor cells immunostain for chromogranin A, CD56, neuron specific enolase, and, as in this case, synaptophysin.

NET of the cervix demonstrates clinical and biological findings found in both squamous endocervical carcinoma and NETs in general, making it a unique entity (Bifulco *et al.* 2009). They are specifically classified into large cell NET, small cell NET, typical carcinoid cells, and atypical carcinoid tumor (Mannion *et al.* 1998). With features similar to small cell lung cancer, small cell NETs are associated with an aggressive lethal clinical course (Albores-Saavedra *et al.* 1997; Conner *et al.* 2002).

NET of the cervix is more aggressive and carries a more deadly prognosis than squamous cell cervical cancer of the cervix. The five-year survival of NET of the cervix was 35.7%, much worse than that of squamous carcinoma (60.5%) and adenocarcinoma (69.7%) (Chen *et al.* 2008). NET of the cervix is more likely to metastasize to lymph nodes, invade adjacent organs, and have hematogenous spread as seen in our index patient. They are characterized by a high mitotic rate and extensive necrosis (Ambros *et al.* 1991; Stoler *et al.* 1991).

The incidence of cervical cancer in the United States ranges from 7.7–12.5/100,000 (Tarver, 2012). Invasive cervical cancer develops from cervical intraepithelial neoplasia; a progression that takes years to occur. This lengthy progression provides an opportunity to detect this cancer at an earlier stage using screening methods; the Papanicolaou (PAP) smear is widely used as a screening tool for cervical cancer (Holowaty *et al.* 1999). The sensitivity of the PAP smear is variable, 55–80%, due to the fact that there is no gold standard test for comparison to the PAP smear. The sensitivity is suggested to be higher because of the slow rate of cancer progression (Benoit *et al.* 1984; Soost *et al.* 1991). The risk of progression from mild to severe dysplasia or worse was only 1% per year, while the risk of progression from moderate dysplasia was 16% within two years and 25% within five years (Holowaty *et al.* 1999). Due to the slow rate of disease progression, screening for cervical cancer is recommended every three years for women from twenty-one to sixty-five years old, using PAP smear, or a combination of PAP and HPV testing every five years. The presentation of NETs of the cervix are variable including vaginal bleeding, pelvic pain and pressure, weight loss, and few are found on PAP smear. They sometimes present with malignant ascites (Cohen *et al.* 2010). As in our case, a cervical mass can be identified in the majority of the cases at the time of presentation. Given the rarity of this tumor, there is no

unanimous agreement on treatment (Hirahatake *et al.* 1990; McCusker *et al.* 2003; Sevin *et al.* 1996; Viswanathan *et al.* 2004).

Lynch syndrome is an inherited cancer syndrome associated with MSI that can result in tumors occurring commonly in the colon, endometrium, ureters, ovaries, as well as other organs (American Gastroenterological Assocation, 2001). Recently the spectrum of the syndrome has increased to include sarcoma (Brieger *et al.* 2011; Sijmons *et al.* 2000), leiomyosarcoma (Clyne *et al.* 2009; Nilbert *et al.* 2009; Yu *et al.* 2009) and liposarcoma (Nilbert *et al.* 2009), melanoma (Ponti *et al.* 2008), and epithelial malignancies of organs such as the breast (D'Arcy *et al.* 2011), prostate (Soravia *et al.* 2003), lung (Nolan *et al.* 2009), thyroid (Chen *et al.* 2008), and adrenal cortex (Berends *et al.* 2000; Broaddus *et al.* 2004; Medina-Arana *et al.* 2011). This syndrome is caused by loss one of many the DNA MMR protein. The role of DNA MMR proteins is to maintain the integrity of the cell's genome by correcting errors in pairing mismatch during DNA replication (Wu *et al.* 2001). These proteins work with other proteins to produce heterodimeric recognition complexes and heterodimeric repair complexes to correct DNA mismatch during DNA replication. Loss of MMR protein expression leads to ineffective DNA MMR which contributes to MSI and cancer formation (Kolodner *et al.* 1999). Lynch syndrome should be suspected in individuals who develop cancer at a relatively young age and those with multiple relatives with cancer.

The risk of colon cancer in families with MLH1 and MutS protein homolog 2 (MSH2) mutation is 50–70%, with lifetime cancer risk of almost 80% (including risk of extracolonic cancer) (Bonadona *et al.* 2011; Vasen *et al.* 2007; Watson *et al.* 2008). All family members of our case tested positive for the MLH1 mutation. DNA MMR proteins are expressed in all cells of the human body, but they have been linked to an increased risk of certain cancers, mainly of the digestive system (Wilson *et al.* 1995). There have been some studies which attempted to link MSI with pancreatic NETs and intestinal NETs. The results of these studies were inconclusive. One study reported that 10% of pancreatic NETs showed loss of MMR protein expression, another that 33% of insulinomas showed loss of MMR protein expression, while another found only 6% this loss in intestinal NETs and 0% in pancreatic NETs (Arnason *et al.* 2011; Arnold *et al.* 2007; House *et al.* 2003).

Our case demonstrates MSI in an individual with known Lynch syndrome who presented NET of the cervix. This raises the question of the causal relationship of MSI and the development cervical NET in the current case. The unusual presentation of NET in our case as the first malignancy in a patient with Lynch syndrome is rare. This is the third reported case of which we are aware. The first was NET of prostate showing MSH2 MSI and loss of MSH2 expression (Wagner *et al.* 2010), and the second was a pancreatic NET showing

loss of expression of MSH2/MSH6 (Karamurzin *et al.* 2012). This suggests that a new approach to screening is needed in patients with Lynch syndrome, to include MMR expression, MSI and DNA MMR protein defects. NETs are rare cancer of the female genital tract, with an aggressive clinical course and poor outcome. More studies are needed on NET in the presence of Lynch syndrome to understand the role of MSI and DNA MMR proteins in the pathogenesis of NET.

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