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CASE REPORT

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Large pelvic mass invading into the sacrum: a case report for primary retroperitoneal P16 positive squamous cell carcinoma

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Abstract

Background: This case report reviews a rare form of Human Papilloma Virus (HPV)-associated squamous cell carcinoma—primary retroperitoneal disease. **Case**: A 69-years old female presented to Kingston General Hospital with signs and symptoms concerning for cauda equina and underwent spinal magnetic resonance imaging which demonstrated a multicystic and solid mass invading into her sacrum in addition to significant pelvic lymphadenopathy. An imaging-guided biopsy demonstrated HPV-positive squamous cell carcinoma, of unknown origin. Given the presence of symptomatic disease on initial presentation, she underwent palliative radiation. Once she was discharged in stable condition from hospital, the Gynecologic Oncology team assumed care due to the location of the mass, despite not clearly originating from the cervix. She completed 4 cycles of systemic chemotherapy with carboplatin and paclitaxel. She also received bevacizumab and immunotherapy with pembrolizumab. Over a number of subsequent visits and repeat imaging, there was a drastic reduction of tumour burden in response to this treatment regimen and no evidence of disease progression after 15 months of follow up. **Conclusions**: This is a novel case for retroperitoneal squamous cell carcinoma treated with systemic chemotherapy as well as immunotherapy resulting in a significant treatment response.

Keywords

Squamous cell carcinoma; Human papilloma virus; Retroperitoneum

1. Introduction

Cancer of unknown primary (CUP) is the sixth to eighth most common malignancy and accounts for approximately 2–5% of new cancer diagnoses worldwide [1]. Squamous cell carcinoma (SCC) represents 5–8% of CUP histologic subtypes and is most often associated with HPV positivity [1]. There has only been a few cases published in the literature demonstrating primary retroperitoneal squamous cell carcinoma making this a very rare occurrence. Matsuzaka *et al*. [2], describe 7 cases in the literature of primary retroperitoneal SCC and 6 of these cases were positive for either P16 or HPV. Four of the seven cases discussed also had a past history of hysterectomy, which was thought to be a contributing factor [2]. However, here we report a case of a healthy 69 year-old female with P16 positive squamous cell carcinoma originating from the retroperitoneum without a past history of cervical or vaginal dysplasia.

2. Case report

A 69 years old healthy female initially presented to the Emergency Department at Kingston General Hospital with signs and symptoms concerning for cauda equina. She had experienced a 2–3 months history of low back pain prior to her presentation, which progressively worsened despite conservative management and pharmacologic analgesia. She then started to experience paresthesia and numbness in the posterior perineum after voiding. She did not have any urinary retention, however she did report significant constipation, which was thought to be due to excessive use of narcotic medications. On neurological assessment, she had equal strength of her upper limbs, however her lower limbs there was decreased strength (3/5) and sensation (4/5) to the left lower limb. She was able to ambulate, but required a walker and assistance compared to her previous baseline where she was mostly independent. Given these concerning features, she underwent an urgent spinal Magnetic resonance imaging (MRI) (Fig. 1) which demonstrated a lytic lesion involving the presacral region permeating the sacral bone extending to the sacral canal in the median and left paramedian position with encasement of the left sacral nerve roots. Anteriorly the lesion extended along the left lateral aspect of the sacrum, behind the left common iliac artery and compared to previous spine MRI completed November 2022, the lesion had increased in size. There was evidence of significant pathological lymphadenopathy surrounding the aorta (2.9 cm para-aortic lymph node seen on spinal MRI) as

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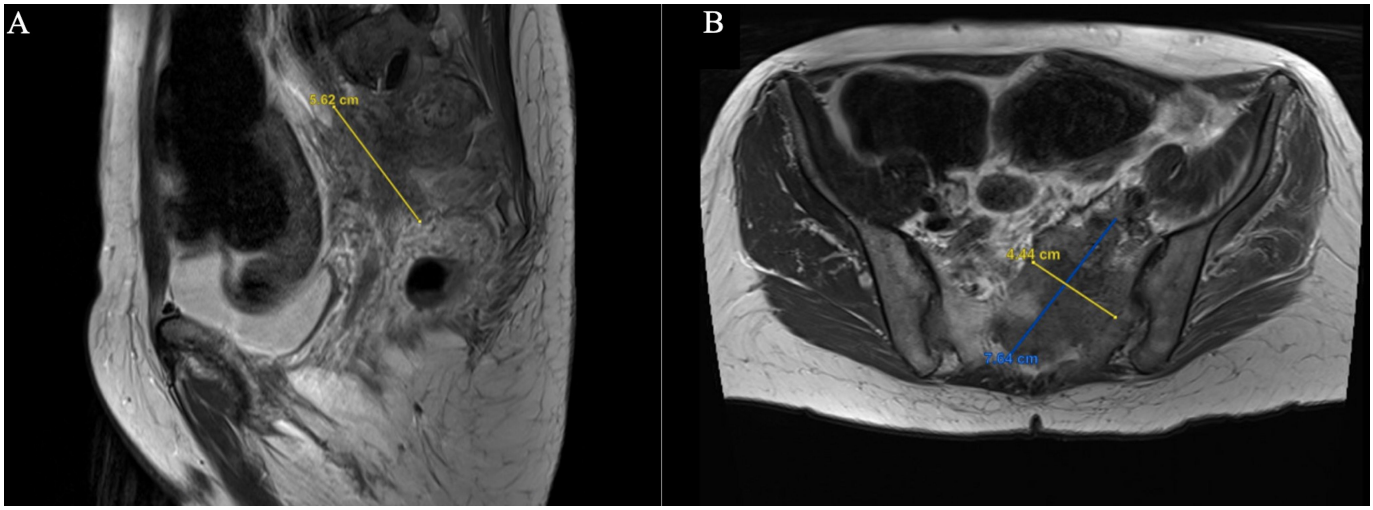

FIGURE 1. Urgent spinal MRI upon initial presentation to the emergency department. (A) Sagittal view of pelvic MRI demonstrating a 5.6 cm pelvic mass adjacent to the left hemisacrum. (B) Axial view of pelvic MRI with additional dimensions of pre-sacral mass at 4.4 cm and 7.6 cm in maximal diameter.

well as lymphadenopathy within the pelvis.

Given the concerns for malignancy, she was referred to Interventional Radiology immediately and underwent an imaging-guided biopsy within a few hours from presentation to hospital. The biopsy was taken from the left para-aortic lymph node, which was the easiest to access. While awaiting these biopsy results, she was admitted to hospital for observation and close monitoring for progression of her symptoms in case urgent intervention was necessary. Tumour markers for common gynecologic and ovarian pathologies, including Cancer Antigen (CA)-125, Carcinoembryonic Antigen (CEA) and CA19-9 were drawn and within normal limits. She continued to complain of significant left-sided leg pain and weakness as well as posterior perineal numbness and constipation. She did not have issues voiding or urinary retention. Her medications were optimized while in hospital to address her pain and constipation concerns. The Orthopedic Spinal team was consulted initially and involved in her care to assess whether immediate spinal decompression would be necessary to prevent complete cauda equina. However, given that her symptoms remained relatively stable over a few days and that this was likely a slow-growing process, the Spinal service did not feel surgical intervention was necessary. Eventually, her biopsy results returned as squamous cell carcinoma and positive for P16, CK-pan, P40 and P63 by immunohistochemistry. With this new information, she underwent a very thorough physical exam while admitted to hospital to identify a possible origin. The oral mucosa, skin, vulva, cervix and anus were all clear for any concerning lesions. A Pap was completed and normal. Further imaging was also completed for staging. A computed tomography (CT) abdo/pelvis showed the same pre-sacral mass measuring 5.0 × 5.6 × 6.8 cm in size with associated with left para-aortic and iliac lymphadenopathy as well as left renal hydronephrosis likely due to left ureteric compression. A CT chest demonstrated 2 small nodules suspicious for malignancy measuring 8 mm and 5 mm. On pelvic MRI, the sacral mass appeared separate from gynecologic structures (uterus, cervix) and gastrointestinal tract (rectum, sigmoid colon). Therefore, given that there was no clear source identified, it was considered a primary retroperitoneal SCC.

Given the sacral invasion, she was offered palliative radiation therapy for immediate symptom control. She received 20 Gy in 5 fractions. Once this was complete, she was discharged from hospital and underwent a positron-emission-tomography (PET) scan (Fig. 2).

This PET scan showed fluorodeoxyglucose (FDG) avidity in the known left pelvic mass involving and invading into the left hemisacrum and sacral body with epidural extension to the neural foramen. It also showed metabolic early activity in the retrocaval, left para-aortic, left external iliac, left hilar adenopathy in keeping with metastasis along with multiple FDG avid pulmonary nodules and a solitary segment 3 liver lesion in keeping with visceral metastases.

Given the rarity of a primary retroperitoneal SCC, there is no established treatment regimen. Due to the location of this mass, it was presumed to be gynecologic in origin and therefore systemic chemotherapy with carboplatin and paclitaxel was initiated. After the first cycle of chemotherapy, the patient developed a left leg deep vein thrombosis (DVT), which was also treated and she remained on anticoagulation. Due to the metastatic nature of her disease, bevacizumab was added in addition to chemotherapy at the time of her third cycle of carboplatin and paclitaxel. The pathology from her biopsy was also reassessed and found to be HPV16 positive and have a programmed cell death ligand (PDL) score that was >1. Unfortunately, prior to her fourth cycle of chemotherapy with bevacizumab and planned addition of pembrolizumab, the patient developed significant neutropenia requiring granulocyte stimulating factor (G-CSF) and had a 20% dose reduction of paclitaxel.

In the interm, she had a repeat CT scan approximately 6 months following initial presentation which demonstrated significant treatment response (after her third cycle of carbo/taxol and one cycle of bev), with reduction in the size of the primary mass (4.7 × 4.1 × 3.8 cm *vs.* 5.0 × 5.6 × 6.8 cm) along with

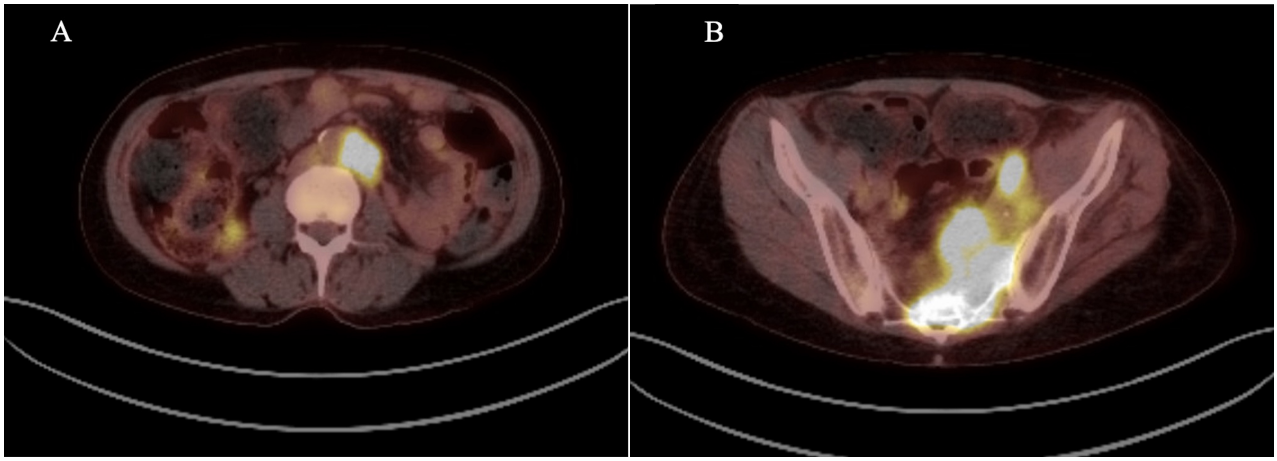

FIGURE 2. Initial Positron-Emission-Tomography (PET) scan showing fluorodeoxyglucose avidity. (A) Clear FDG avidity at the level of the para-aortic lymph nodes. (B) FDG avidity in the left-hemi pelvis correlating to pelvic mass as well as pelvic lymph nodes seen on CT and MRI scans.

resolution of pulmonary nodules and liver lesion as well as resolution of para-aortic and pelvic lymphadenopathy.

Once she recovered from neutropenia, she completed a fourth cycle of chemotherapy including the first cycle of immunotherapy, pembrolizumab; a PDL-1 blockade agent. She is now on maintenance bevacizumab and pembrolizumab and her most recent follow up imaging in May 2024 and October 2024 reported stable disease without any evidence of progression. Her symptoms have mostly resolved and her left leg weakness is gradually improving with time. She is now engaging in more physical activities and we are very optimistic about her future.

3. Discussion

Primary retroperitoneal squamous cell carcinoma is a rare occurrence with only a few case reports published world-wide. Table 1 (Ref. [3–14]) provides an overview of details related to these cases. The total number of cases we have included in our review is 21. The average age at diagnosis was 55.1 (27–76) and the most common underlying factor contributing to the squamous histology was P16 positivity at 80.95% of cases (17/21). Many of these cases presented with lower limb abnormalities, including deep vein thrombosis, edema, weakness or unilateral pelvic pain. Upon further investigation, imaging revealed a pelvic or retroperitoneal mass that was then confirmed to be squamous cell carcinoma histology without any evidence of a primary source. In such cases, patients may need to undergo exploratory laparotomy to obtain accurate biopsy sampling or other imagining modalities, such as a PET-FDG scan [2]. Although, PET scans have widely been used for cancers of unknown primary, many cases were still not able to determine the precise source for SCC when initially found in the retropertonium.

The pathogenesis of retroperitoneal SCC is still unknown. Schatz *et al*. [15] suggest a possible theory of squamous metaplasia from embryonic rests due to chronic peritoneal irritation. Due to the high presence of HPV-positivity in cases of primary retroperitoneal squamous cell carcinoma, it is possible there is a direct exposure of the retroperitoneum to HPV via genital or anal infectivity. HPV is highly associated with cervical (90%) and anal (95%) cancers, as well as significant percentage of vulvar, vaginal and oropharyngeal cancers [2]. It is unclear exactly how HPV can be transmitted to the retroperitoneum, however there has been proposed mechanisms including hematological or lymphatic spread from microinvasive disease present elsewhere [10]. HPV can lead to the development of low-grade and high-grade lesions which may impact their infectivity. Low grade lesions result in formation of new viral particles, whereas high-grade lesions are due to HPV genome integrating into the host genome to affect expression of E6 and E7 oncogenes [10]. Therefore, presence of microscopic high-grade cervical lesions, which are not visible on imaging or physical exam, can potentially metastasize to other locations, including the retroperitoneum. Other possible explanations include synchronous HPV-dysplastic lesions, suggesting independent infectivity at different anatomical locations as well as retrograde dissemination from the cervix and uterus into the retroperitoneal space via direct contact with the peritoneal membrane [10]. These explanations focus on microscopic disease present elsewhere, however there is a rare possibility that squamous cell carcinoma may develop in the retroperitoneum without other areas of microinvasive disease. The pathogenesis of this is difficult to theorize given the direct nature of HPV infectivity. Chen *et al*. [16], suggest these tumours potentially develop from serous or mucinous metaplasia of the pre-existing retroperitoneal coelomic mesothelium.

As shown in Table 1, there are documented cases of non-HPV P16+ primary retroperitoneal SCC. Clements *et al*. [5], demonstrated a case of HPV negative/P16+ retroperitoneal SCC that was managed with primary chemoradiation, however ultimately had progression of disease. Cucinella *et al*. [11], reported a case of primary retroperitoneal SCC on the background of endometriosis. While the tumour was positive for P16, it was negative for HPV. This patient had adjuvant chemotherapy following surgical excision and was disease-free at 6 months following diagnosis [11]. From our literature review, these are the only 2 cases of HPV negative primary

TABLE 1. Review of primary retroperitoneal SCC cases.

Authors	Case	Patier age	Disease presentation and tumour location	HPV/P16 Status	Treatment	Follow up duration	Outcomes
Khalil *et al.* [3], 2005	1	57F	Pelvic pain and constipation. CT and MRI demonsrated 6 cm multicystic mass within the rectovaginal septum	Unknown	Exploratory laparotomy with surgical resection, adjuvant chemotherapy (cisplatin and 5-FU)	6 mon	Recurred while on treatment and died of disease
Matsuyama *et al.* [4], 2006	2	70F	Right-leg edema and CT finding of right-sided retroperitoneal mass	Unknown	Primary resection and adjuvant radiation	17 mon	No evidence of disease
Clements *et al.* [5], 2010	3	34F	Presented with DVT and mass identified in R psoas	HPV−/P16+	Primary chemoradiation (cisplatin)	23 mon	Progressive disease at cervix, alive at 23 mon
Clements *et al.* [5], 2010	4	27F	Presented with DVT and mass identified in the L psoas	HPV unknown/P16+	Neoadjuvant chemotherapy with local progression, followed by chemoradiation	12 mon	Died of disease
Clements *et al.* [5], 2010	5	43F	Imaging revealed mass in L psoas	HPV+/P16+	Palliative radiation	12 mon	Progression of disease to lymph nodes
Clements *et al.* [5], 2010	6	44F	Presented with DVT and mass identified in L psoas	HPV+/P16+	Paclitaxel or carboplatin chemotherapy followed by chemoradiation	6 mon	No evidence of recurrence
Clements *et al.* [5], 2010	7	52F	Presented with DVT and mass identified in R psoas	HPV+/P16+	Palliative pelvic radiation	8 mon	Died of disease
Clements *et al.* [5], 2010	8	54F	Right-sided lymphadenopathy	HPV+/P16+	Surgical resection followed by 9 chemoradiation (using carboplatin)	24 mon	Died of disease
Ryu *et al.* [6], 2012	9	66F	Right leg edema and inguinal pain. MRI showed right-sided retroperitoneal mass and lymphadenopathy	Unknown	Concurrent chemoradiation with paclitaxel and carboplatin and three additional cycles of chemotherapy	48 mon	No evidence of recurrence
Oh *et al.* [7], 2015	10	56F	Incidental finding of left-sided retroperitoneal mass on US imaging	HPV 18+	Surgical resection and adjuvant chemotherapy (5-FU and cisplatin)	1 mon	No evidence of recurrence
Ahdallah *et al.* [8], 2016	11	64F	Acute-onset lower abdominal pain with MRI demonstrating mass near left greater siatic foramen and involving sacral nerve roots	HPV unknown/P16+	Primary chemotherapy with paclitaxel and carboplatin followed by chemoradiation (5-FU protocol)	N/A	N/A
Isbell and Fields *et al.* [9], 2016	12	69F	Incidental finding of left-sided retroperitoneal mass while being investigated for metastatic lymphoma	HPV unknown/P16+	Primary chemoradiation with weekly cisplatin	7 mon	No evidence of recurrence
Isbell and Fields *et al.* [9], 2016	13	58F	Left-sided hip pain with CT demonstrating left retroperitoneal mass	HPV unknown/P16+	Cytoreductive surgery with adjuvant chemoradiation (weekly cisplatin)	48 mon	No evidence of recurrence

TABLE 1. Continued.

Authors	Case	Patier age	Disease presentation and tumour location	HPV/P16 Status	Treatment	Follow up duration	Outcomes
Isbell and Fields *et al*. [9], 2016	14	47F	Left-leg pain and CT demonstrating a left pelvic side wall mass	HPV unknown/P16+	Patient declined treatment	12 mon	Died from disease
Agrawal *et al*. [10], 2016	15	50F	Right leg DVT with right hip and leg pain. CT and MRI showed right-sided retroperitoneal mass	HPV unknown/P16+	Primary chemoradiation with weekly cisplatin	22 mon	Recurrent disease with multiple enlarged nodes
Matsuzaka *et al*. [2], 2019	16	76F	Anal pain with CT demonstrating large cystic mass thought to be originating from the left adnexa. Later found to be in the retroperitoneal cavity	HPV+/P16+	5 cycles of neoadjuvant chemotherapy (paclitaxel and carboplatin), interval debulking surgery and 3 cycles of adjuvant chemotherapy	6 mon	No evidence of disease
Cucinella *et al*. [11], 2022	17	52F	Incidental finding of retroperitoneal para-rectal mass on routine exam	HPV−/P16+	Surgical resection of mass with endometriotic nodules. 6 cycles of adjuvant chemotherapy (carboplatin and paclitaxel)	6 mon	No evidence of disease
Zhu *et al*. [12], 2023	18	43F	Right-sided lumbosacral pain with CT demonstrating right adnexal mass and multiple retroperitoneal metastases	HPV unknown/P16+	Cytoreductive surgery with adjuvant chemotherapy (paclitaxel and nedaplatin)	72 mon	No evidence of recurrence
Matylevich *et al*. [13], 2024	19	62F	Routine surveillance following surgical treatment for endometrial cancer. CT showed 6.8 cm mass near pelvic floor	HPV+/P16+	Surgically resected, margins negative. No requirement for adjuvant therapy	14 mon	No evidence of disease
Koge *et al*. [14], 2024	20	64F	Large osteolytic pelvic mass	HPV unknown/P16+	Palliative radiation and nivolumab	7 mon	Progression-free survival for 7 mon
Current case	21	69F	Lower back pain with perineal numbness and left lower leg weakness	HPV+/P16+	Primary chemoradiation with maintenance pemrolizumab	16 mon	Stable disease without recurrence or progression

HPV: Human Papilloma Virus; CT: Computed tomography; MRI: Magnetic resonance imaging; 5-FU: 5-Fluorourocil; DVT: Deep vein thrombosis; F: female; N/A: not applicable.

retroperitoneal SCC documented. Therefore, it is difficult to determine the prognosis related to these types of cases. Despite many cases not having HPV testing completed, there is a strong correlation between P16 positivity and HPV-related disease. In our case, the tumour was tested and found to be HPV16 positive.

When comparing primary cervical, vaginal or vulvar SCC, retroperitoneal disease seems to closely mimic that of cervical SCC. Based on our literature review, most patients have disease present in the lower pelvis with direct extension of the tumour within the pelvic sidewalls, contributing to hydronephrosis or lower limb symptomatology. In addition to direct extension, there is often pelvic or paraaortic lymphadenopathy present at the time of diagnosis. Although it is challenging to fully understand outcomes for retroperitoneal SCC compared to SCC originating from other gynecologic structures due to clinical heterogeneity, there does appear to be some similarities which may be explained by HPV-related mechanisms of disease.

Once diagnosed, prognosis is difficult to determine based on lack of existing data. Based on our literature review, it appears 57.1% (12/21) of cases had no evidence of recurrent or progressive disease after an average of 17.5 (1–72) months of follow up. These patients underwent a variety of different treatment modalities as no clear regimen exists. Surgical excision followed by adjuvant chemotherapy or radiation or primary concurrent chemoradiation in non-operable cases remain as a viable option [17]. Similar to early-stage cervical carcinoma, radical hysterectomy with pelvic lymphadenectomy remains a surgical option for disease limited to the pelvis involving uterus and or cervix. For instance, Chen *et al*. [16], demonstrate successful treatment of a primary retroperitoneal SCC after radical hysterectomy, pelvic lymphadenectomy and adjuvant concurrent cisplatin-chemoradiation. Similarly, many cases described in Table 1 have used a combination of surgical excision and systemic therapy, such as chemoradiation or chemotherapy alone. In patients with more advanced disease, the optimal treatment remains unclear. Given that our patient presented with retroperitoneal lymphadenopathy and symptoms related to local invasion of pelvic structures including bone, we started with a short course of radiation therapy for symptomatic control. Following this, we focused on a treatment regimen similar to advanced cervical carcinoma, including paclitaxel and carboplatin chemotherapy as well as bevacizumab. Over the past few years, immunotherapy has shown promising results for patients with advanced gynecologic malignancies including cervical cancer [18]. Pembrolizumab is a humanized monoclonal antibody against PD1 (programmed-death-1) on the surface of T-cells, preventing the interaction between PD1 and PDL-1 (programmed death ligand-1) on tumour cells. This ultimately leads to upregulation of the immune system to target and destroy PDL-1 specific cancer cells. For patients with advanced cervical cancer, Colombo *et al*. [18], demonstrated progression-free and overall survival benefits with the addition of pembroluzimab therapy with or without bevacizumab. Suzuki *et al*. [19], demonstrated effectiveness using pembrolizumab in combination with cisplatin and 5-flurouracil to treat a 32-years old female with metastatic squamous cell carcinoma of unknown primary. Similarly, Koge *et al*. [14], report use of nivolumab in a patient with advanced retroperitoneal SCC following palliative radiation therapy. However, there has not been any published reports using immunotherapy following carboplatin and paclitaxel chemotherapy for advanced primary retroperitoneal squamous cell carcinoma. This case is the first to demonstrate significant disease regression with this treatment regimen including bevacizumab and pebrolizumab combination therapy.

The main limitation of our study is that our observations are based on an individual case. Therefore, we completed an in-depth literature review to determine treatment regimens and outcomes for similar cases published in the literature. However, this may also be prone to publication bias, as cases with less favourable outcomes may not have been reported. The rarity of this disease also makes it challenging to complete high-quality studies or randomized control trials to further understand the prognosis or treatment options. Despite the limitations and potential bias of our case report, we have introduced a novel treatment regimen that may be the starting point for future research for patients with primary retroperitoneal squamous cell carcinoma.

4. Conclusions

Overall, we hope this case inspires further research into the etiology, pathogenesis and appropriate treatment for patients presenting with primary retroperitoneal SCC. Widespread HPV testing may provide more information and detection of these tumours and immunotherapy may play a large role in treatment regimens as it has already shown promise for advanced cervical SCC.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

AD and AA—designed the case report, collected data and wrote the manuscript. AS and AR—contributed to data collection and editorial changes. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The subject has provided consent for us to share this case. The Research Ethics Office at Queen's University has reviewed this Case Report. It has been determined that this project is not considered research and has been granted an exemption.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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