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Case Report Open Access

Promising Tumor Remission After Immunotherapy for Late Relapse of Locally Advanced Cervical Adenocarcinoma Revealed by [18F] Fluoro-2-Deoxy-D-Glucose Positron Emission Tomography

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Abstract

The prognosis of patients with metastatic cervical cancer is poor, with a median survival of 8-13 months. Treatment with chemotherapeutic drugs alone is rarely curative. In the past few years, the development of immunotherapy, targeted therapy, angiogenesis inhibitors, and tyrosine kinase inhibitors has provided better treatment choices for patients with metastatic cervical cancer.

A 52-year-old woman was diagnosed on July 2001, with locally advanced adenocarcinoma of cervix, stage IIb. She underwent concurrent chemoradiotherapy resulting in complete remission for over 10 years. Unfortunately, she was found to have a late relapse of cervical adenocarcinoma with liver metastases (segments 7 and 8) on June 2013. She underwent segmental hepatectomy and cholecystectomy and was transferred to our gynecologic oncology service for standard chemotherapy with immunotherapy based on her immune risk profile (IRP). Immunomodulatory agents, including picibanil (OK-432), interferon-alpha, celecoxib (cyclooxygenase-2 inhibitor), thymalfasin, and aldesleukin (IL-2) were given. Approximately 20 months later, spleen metastasis was suspected by [18F] fluoro-2-deoxy-D-glucose positron emission tomography. The patient underwent gasless laparoscopic intraperitoneal treatment with immunomodulatory agent celecoxib (cyclooxygenase-2 inhibitor) and intraperitoneal immunoviral therapy to create host immunosurveillance for consolidation therapy. Three months later, there was complete remission of the metastatic splenic nodule on repeat imaging.

Our case demonstrates the dramatic promise of immunomodulatory therapy to induce complete remission of a metastatic cancer nodule. This case suggests the potential value of immunotherapy to augment host immunosurveillance to improve survival of metastatic cervical cancer.

Keywords: Cervical cancer; Cervical adenocarcinoma; Metastatic cervical cancer; Liver metastasis; Spleen metastatis; Immunotherapy; [18F] Fluoro-2-deoxy-D-glucose positron emission tomography

Introduction

On a global scale, cervical cancer is the fourth major cancer-related cause of death in women. The majority of women with this cancer are infected by human papillomavirus (HPV). Thus, the infection is highly correlated with all types of cervical cancer (more than 99%), constituting a major public health issue.

As prognosis is related to stage, precise staging via imaging (pre-operatively or following concurrent radiochemotherapy) is key to choosing appropriate therapy. Early-stage cervical cancer is curable in most patients by surgery and/or radiotherapy although they cannot achieve a 100% durable complete response. The 5-year survival rate decreases sharply to 60% to 75% of women with stage II cervical cancer, 30% to 40% with stage III cervical cancer, and 15% or less with stage IV cervical cancer [1].

The treatment for locally advanced cervical cancer remains a challenge. With standard therapy (surgery, radiotherapy, and/or chemotherapy), patients who have invasive cervical cancer still have a greater, 30%, risk of relapse. In one study, HPV DNA was found circulating in peripheral blood of 85% of women following the diagnosis, reflecting the tumor burden and having potential prognostic value [2]. Following the failure of standard therapy, patients are usually given palliative therapy, with 1-year survival of only 15%-20% and 5-year survival of 0%-15%. Thus, we urgently need better therapy for relapse of cervical cancer, and immunotherapy to augment host immunosurveillance may be the way forward. Here, we present a case of cervical adenocarcinoma stage IIB with late relapse at liver metastasis and then spleen metastasis. Our case highlights the clinical

importance of immunotherapy in the case of late relapse of locally advanced cervical adenocarcinoma.

Case Report

This 52-year old woman, G4P3AA1, complained of menorrhagia for more than 5 years. She was followed regularly for what was presumed to be a large adenomyoma. However, an enlarged uterus with progression in myoma size was noted, as was anemia. Laparoscopy was performed on July 2001 to treat the myomas, but a cervical frozen biopsy specimen incidentally found adenocarcinoma. On immunohistochemistry staining, no HPV expression was observed. She was transferred to our Gynecologic Oncology service for management of stage IIb cervical adenocarcinoma. Concurrent chemoradiotherapy was administered, and the patient had a complete remission for more than 10 years. Her immune risk profile (IRP) demonstrated less than 5% to 10% Treg ($CD25^+$ T cells) in circulation following treatment.

However, a liver metastasis tumor (segments 7 and 8) was found in June 2013 by abdominal CT scan (Figure 1). She underwent segmental hepatectomy and cholecystectomy and the final pathology report indicated metastatic adenocarcinoma, most likely of cervical origin. She was transferred to our Gynecologic Oncology service for treatment. In addition to standard chemotherapy, combined immunotherapy was given monthly. The immunomodulatory agents used were picibanil (OK-432), interferon-alpha, celecoxib (cyclooxygenase-2 inhibitor), thymalfasin, and aldesleukin (IL-2). Approximately 20 months later, surveillance with [18F] fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) revealed a splenic nodule suspected to be a metastasis on March 2015 (Figures 2A-2C). We therefore performed gasless laparoscopic operation and inserted an intraperitoneal drainage tube. Hyperthermic lavage (about 4000 ml of lavage solution at 43°C) containing celecoxib and cervarix/gardarsil virus-like particle were given according to priming and booster immunization protocols. Three months later, the splenic nodule had completely disappeared (Figures 2B and 2D).

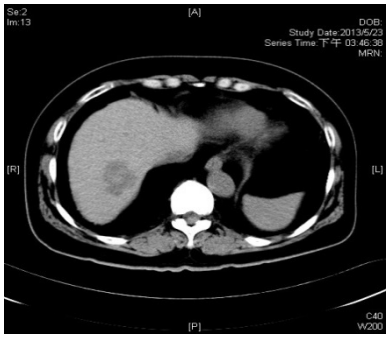

Figure 1: Abdominal CT scan shows liver metastasis tumor at segments 7 and 8.

We follow the patient's serial immune risk profiles (IRP), including of CD3, (common T cells), CD19 (B cells), NK, and immunoregulatory CD25 and $CD11b^+$ immune cells etc. Compared with the IRP before the segmental hepatectomy in June 2013 (Table 1), the postoperative IRP indicated that the patient's host immunogenic potency was restored, as demonstrated by normalization of the CD4/CD8 ratio (from 2.29 to 1.22), reduction in $CD4^+$ T cells from 44% to 35.5%, and enhancement of $CD11b^+$ antigen presenting immune cells 1.3-fold (from 46.7% to 60.1%). But we also found a decrease in B cells from 27.8% to 9.5%. The IRP after compared with before the intraperitoneal treatment for the splenic nodule (Table 2), we found out reducing original sinks (B cells, Tregs, $CD11b^+$) to restore host immune cells' redistribution after intraperitoneal administration of celecoxib and viral-like particle (cervarix and Gardasil). The operative stress rendered host immunosurveillance switch less immunogenicity (CD4/CD8 ratio less than 1) to mimic immunocompromised status.

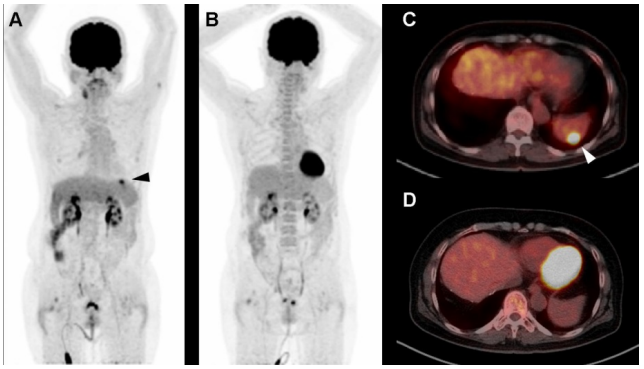

Figure 2: Initial whole body maximum-intensity-projection image (A), and fused (C) of 18F-FDG PET/CT showing an area of increased uptake in the superior border of spleen (arrow head). The lesion disappears after therapy on whole body (B) and fused image (D).

	Oct 12 2012	Jun 27 2013	July 19 2013
	Before IMT (%)	After IMT (%)	After IMT (%)
T-CD3	67.2	70.2	79.2
B-CD19	27.8	9.5	7.3
CD25	3.48	5.36	2.05
$CD4^+CD25^+$	NA	4.46	1.78
$CD154^+$	0.42	0.86	0.29
$CD4^+CD154^+$	0.28	0.2	0.06
$CD11b^+$	46.7	60.1	60.1
$CD83^+CD11b^+$	NA	0.2	0.7
CD4 T Cell	44	35.5	45.2
CD8 T Cell	19.2	29.1	29.6
CD4/CD8	2.29	1.22	1.53
NK-Cell	10	20.5	12.5
CD28	55.6	53.9	61.8
$CD4^+CD28^+$	43.5	34.8	43.7
NKT	0.3	0.4	0.6

Table 1: Immune risk profiles (IRP) comparison before and after segmental hepatectomy and immunomodulatory therapy (IMT).

Following resolution of the splenic nodule, the patient has remained well without further evidence of recurrence until now.

	3. 23 2015	4. 24 2015	10. 29 2015
	Before IMT (%)	After IMT (%)	After IMT (%)
T-CD3	49	61.4	55.6
B-CD19	20.7	14.7	24.3
CD25	4.93	2.92	2.26
$CD4^+CD25^+$	4.38	2.44	1.92
$CD154^+$	0.46	0.64	0.7
$CD4^+CD154^+$	0.28	0.26	NA
$CD11b^+$	42.48	11.1	32.7
$CD8^+CD11b^+$	7.4	0.96	12.2
CD4 T Cell	29.6	21.5	20.5
CD8 T Cell	25.5	36.2	34
CD4/CD8	1.16	0.59	0.6
NK-Cell	28.3	17.3	21.5
CD28	34.5	25.3	26.3
$CD4+CD28^+$	22.7	18.7	17.4
NKT	0.2	0.4	0.8

Table 2: Immune risk profiles (IRP) comparison before and after the gasless laparoscopic operation with immunomodulatory therapy (IMT) by intraperitoneal celecoxib (cyclooxygenase-2 inhibitor) and virotherapy.

Discussion

Cervical cancer is one of the major cancer types for which new immune-based cancer treatments are currently under development. Several approaches to T-cell based-immunotherapy for cervical cancer have shown promise in early clinical trials. The addition of adjuvants, cytokines, and vaccine protocols to conventional therapies is designed to stimulate the innate and adaptive immune cells to generate an efficient anticancer response therefore, to achieve a durable complete remission [3].

HPV16-negativity and extravaginal relapse of cervical cancer were significant poor prognostic factors [4]. In our patient with stage IIb cervical adenocarcinoma, she had late relapse in liver and then spleen metastasis. The liver metastatic tumor successfully remission after surgery, chemotherapy combined with immunothereapy. After the therapy, regular surveillance with FDG-PET is helpful to identify possible metastatic lesions [5,6]. In our case, the spleen metastatic tumor was identified by FDG-PET, and the spleen tumor has successful remission after immunotherapy.

To generate potent anticancer immunity, antigen-presenting cells, most notably dendritic cells (DCs), must undergo a number of processes. We used adjuvant picibanil (OK-432) to trigger skin naïve DCs to immature DCs to present major histocompatibility complex (MHC) class I and/or Class II, Toll-like receptors or FcR receptor to capture of tumor associated antigens within in situ *in vivo* immunization. Mature DCs secrete multiple chemokines and/or cytokines to recruit innate and adaptive immune cells to produce an anticancer response. On the other hand, an efficient long-term $CD8^+$ T-cell anticancer response requires $CD4^+$ T cells help to maintain host immunosurveillance [7-10]. When the spleen metastasis was found, we performed gasless laparoscopic operation and instilled intraperitoneal hyperthermic lavage with celecoxib and cervarix/gardarsil virus-like particle. We used a vaccination protocol to enhance a burst of $CD4^+$ T cells and/or $CD8^+$ T cells. The purpose of vaccination protocols is delivery of tumor-associated antigens to antigen-presentation cells concurrent with the activation of the immune cells.

About the IRP in our patient, we evaluated at least three components. Stimulatory molecules included CD28 (naïve or juvenile marker), CD40L (CD154), NK etc. Inhibitory molecules included B cells (CD19), CD25, NKT etc. Finally, immunosuppressive and/or immunoregulatory molecules included $CD4^+CD25^+$T cells, $CD11b^+$ (myeloid derived suppressive cells) etc. The purpose of monitoring the patient's IRP is to evaluate host immunosurveillance (i.e., elimination of host's circulating cancer cells) to achieve a durable complete response.

In conclusion, our case highlights the clinical significance of immunotherapy in case of late relapse of locally advanced cervical adenocarcinoma.

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