Immunological aspects of conventional and new treatments for cervical cancer, an immunopharmacological approach

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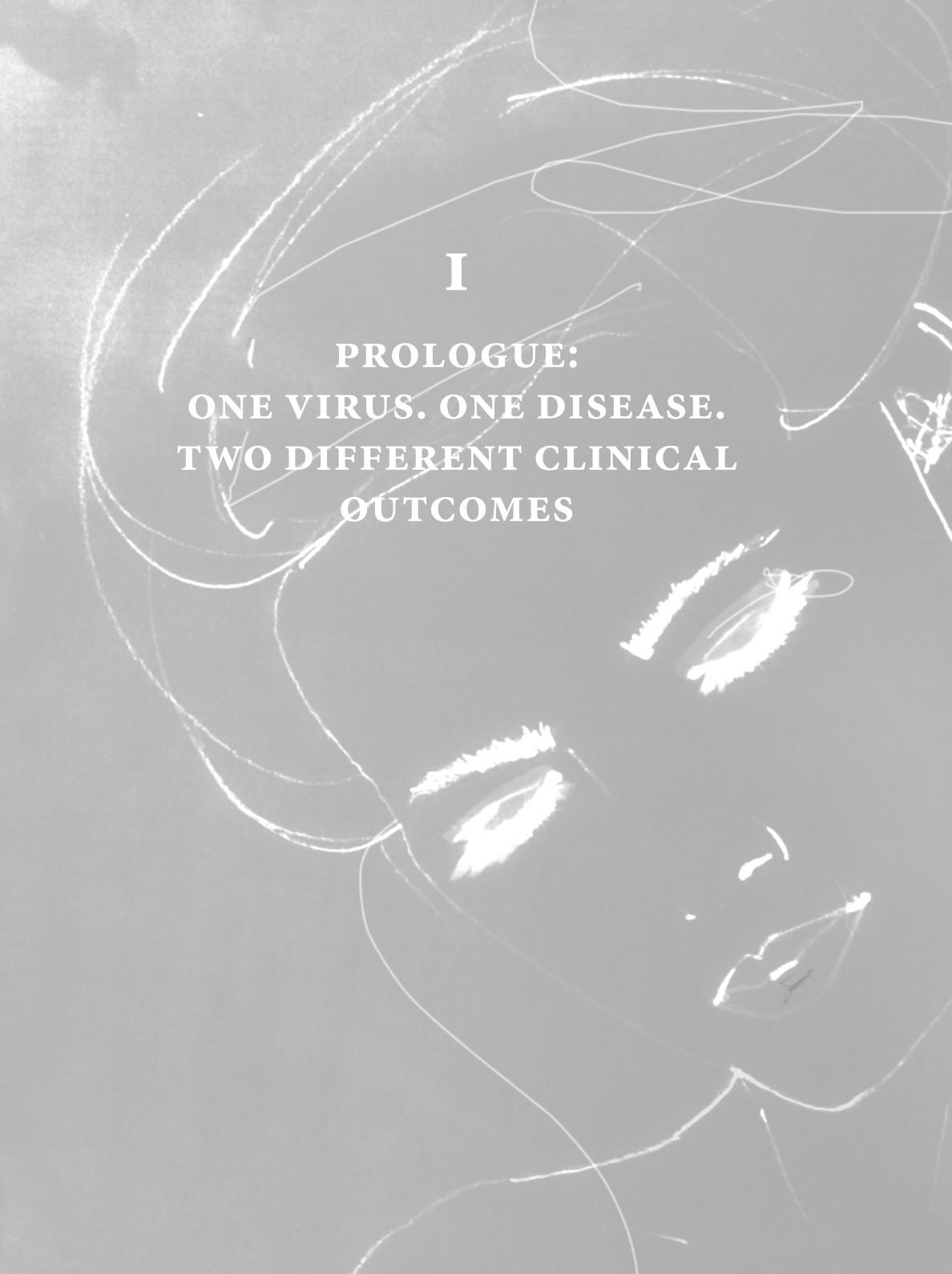

I

PROLOGUE: ONE VIRUS. ONE DISEASE. TWO DIFFERENT CLINICAL OUTCOMES

A 43 year old Caucasian woman was referred to the Leiden University Medical Center (LUMC) with FIGO (International Federation of Gynecology and Obstetrics) stage Ib1 cervical cancer. For more than 10 years, she had nonspecific complaints of abdominal pain, for which no medical cause was found. The cervix bled easily at routine gynecological examination. A Papanicolaou (Pap) smear revealed a Pap 5 and biopsies showed a moderately differentiated squamous cell carcinoma of the cervix. The patient was scheduled for a radical hysterectomy with bilateral pelvic lymph node dissection. During surgery, frozen section analysis of a suspicious and enlarged lymph node along the left external iliac artery was found to be tumor positive. Histopathological examination of the surgical specimen showed a non-keratinizing squamous cell carcinoma with a maximal diameter of 27 mm and a maximal infiltration depth of 11 mm. There was extensive lympho-vascular space involvement (LVSI) and the surgical margins at the vaginal cuff were tumor positive. Of the 14 lymph nodes that were removed, 2 turned out to be tumor positive. Human Papilloma Virus (HPV) analysis demonstrated the presence of the high-risk HPV type 16 in the tumor. Because of lymph node metastases and tumor positive surgical margins, it was decided to treat the patient with adjuvant chemo-radiation. She received 46 gray (Gy) external beam radiation therapy (EBRT) with concurrent cisplatin chemotherapy at a dose of 40 mg/m^2 and brachytherapy (BT) boost.

Two years and 4 months after primary treatment, she suffered from severe abdominal pain and dyspnea. Computer tomography (CT) showed extensive metastatic disease with metastases in the liver and bone, enlarged retroperitoneal and mesenteric lymph nodes, carcinomatous pericarditis and pleuritis, and unilateral hydronephrosis. Histopathological examination of pericardial fluid confirmed metastatic cervical cancer. The patient participated in a phase I/II trial and was treated with palliative chemotherapy (6 cycles of carboplatin and paclitaxel) in combination with HPV16 Synthetic Long Peptide (SLP) vaccination which was administered 2 weeks after the 2nd cycle of chemotherapy. The CT scan performed after the 3rd cycle of chemotherapy showed regression of the tumor according to the Response Evaluation Criteria in Solid Tumors (RECIST), and stable disease until 3 months after the last cycle of chemotherapy. However, 5 months after completion of the chemotherapeutic treatment, she developed progressive disease with malignant lymphadenopathy, new liver metastases and extensive pleural and pericardial fluid. Despite experimental treatment with dendritic cell therapy abroad, and local pericardial bleomycine injection, she died at the age of 46, due to progressive cervical cancer.

Around the same time, a 33 year old Caucasian woman was presented at the outpatient clinic of the department of Gynecology with complaints of irregular

vaginal blood loss. Standard cervical cancer screening with Pap smears had not been performed previously. At clinical examination, she was found to have a cervical mass, which was biopsied and diagnosed as a squamous cell carcinoma of the cervix, clinically FIGO stage Ib1. Because of her wish to preserve fertility, the patient was scheduled for an abdominal radical trachelectomy with pelvic lymphadenectomy. During surgery, trachelectomy specimens were submitted for frozen section. Unfortunately, the surgical margin was grossly tumor positive and a conversion to radical hysterectomy was performed. Histopathological characteristics revealed a keratinizing squamous cell carcinoma with a maximal tumor diameter of 30 mm, a circumferential growing pattern and a tumor infiltration depth of 17 mm, that reached the serosa. There was no parametrial involvement, no LVSI, and 27 lymph nodes were removed none of which was tumor positive. HPV analysis demonstrated the presence of the high-risk HPV type 16 in the tumor. Because of the transmural growth to the serosal surface at the region of the endocervix and lower uterine segment, the patients was treated with EBRT to the paracervical and parametrial region.

Six months later, magnetic resonance imaging was performed because of complaints of pain in the back and the thigh. This examination revealed a 20 x 17 mm lesion, suspect for metastasis of the cervical tumor, located at the right obturator foramen and with signs of involvement of the sigmoid colon. There were no signs of other distant metastases. Clinical examination showed no signs of local recurrence, and no enlarged lymph nodes. After multidisciplinary consultation, she was surgically treated with complete removal of the tumor and a resection of the adjacent sigmoid colon. Histopathological examination confirmed localization of the squamous cell carcinoma of the cervix, with growth in the connective tissue into the circumferential margin; there was no growth into the colon. Because of the microscopically involved surgical margin, the patient was treated with concurrent chemoradiation to the area of the recurrence and common iliac lymph node regions. Concurrent chemotherapy with 5 cycles of cisplatin at a dose of 40 mg/m^2 was administered. Despite the postoperative and systemic morbidities, the intensive treatments were well tolerated and complete response was achieved. Follow-up was alternately performed by the radiation oncologist and a gynecologic oncologist every 3 months. Until 18 months after first recurrence, consultations showed no signs of recurrent disease.

These cases present 2 patients suffering from the same malignancy, but with a different course of disease and outcome. Differences in clinical presentation, treatment modalities, tumor responses and clinical outcome motivate clinicians and researchers to combine their knowledge from different (bio)medical

specialties as gynecology, oncology, radiotherapy, pathology, immunology and pharmacology. Apparently, a multitude of mechanisms is responsible for either the tumor susceptibility or the escape from aggressive treatment modalities. The cases show that not a single cervical cancer patient is the same, and clinical response depends on more than only the kind of tumor. The burning *'how come'* and *'why'* questions within these cases formed the basis of this thesis.