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Case Report

Multiple Tumor Induction after Treatment of Temporal Arteritis with Prednisone

Frank F. Piraino

Keywords
Temporal arteritis · Prednisone · Drug side effects · Inflammation · Autoimmune disease · Adenocarcinomas · Mutations · Cancer immunity

Abstract
A 74-year-old female was diagnosed with the autoimmune inflammatory disease temporal arteritis and treated with high and low doses of prednisone over a period of 6 years. During that time, she developed cancers of the lung and colon as well as a soft tumor mass on lumbar vertebrate L3. She also experienced a series of debilitating and disabling symptoms while on prednisone treatment. A temporal analysis of the association of prednisone therapy and immune markers to the successive appearance of the malignant tumors strongly suggests that in the absence of a functioning natural immune and surveillance system by treatment with the immune knockout drug prednisone, spontaneous, multiple independent mutations occurred in several sites in the organ systems of this patient. Over a period of time, these developed into malignant cancers, including a lung nodule which became cancerous 256 days later, as well as the cancers of the colon and a soft tumor mass on lumbar vertebrate L3.

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Frank F. Piraino, PhD
517 Rupert Road
Waunakee, WI 53597 (USA)
E-Mail fpiraino@wisc.edu

Introduction

Temporal arteritis (giant cell arteritis, TA) is an inflammatory autoimmune disease of devastating, extremely painful and sometimes fatal consequence. It is the commonest form of systemic large vessel vasculitis that may occur anywhere in the body. Pathologically, it is characterized by invasion of large blood vessels by giant mononuclear cells that promote damage to actin and elastin proteins in the lamella of blood vessels. The symptoms are caused by local ischemia due to endovascular damage and cytokine-mediated changes that include systemic vasculitis, blindness, severe head pain, generalized polymyalgia rheumatic, and aortic stenosis [1].

Prednisone is the most commonly prescribed oral drug used in the treatment of TA and other autoimmune diseases. It is a corticosteroid synthetic drug that is effective as an immunosuppressant. It prevents the release of cytokines, interferons, interleukins, substances in the body that regulate the inflammation reaction and it results in the almost complete suppression of both natural and humoral immunity. It is usually the first drug of choice in the treatment of many severe inflammatory conditions including transplant rejection, autoimmune disease, and some forms of cancer. Prednisone is metabolized in the liver to its active form prednisolone and is roughly 4 times as potent as naturally occurring glucocorticoids. Glucocorticoid hormones synthesized in the adrenal cortex prevent or suppress inflammation and immune responses. At the molecular level, they cross cell membranes and bind to specific cytoplasmic receptors. This binding modifies transcription and ultimately protein synthesis. These actions include inhibition of leukocyte infiltration to the sites of inflammation and interference in the function of mediators of inflammatory and humoral immune responses. The net clinical effect is a general suppression of the immune process [2, 3].

Long-term use of high doses of prednisone cause a variety of physically disabling and psychological disorders as side effects. Physical changes include edema of the face (moon face), edema of the legs and ankles, fatty deposits in the neck and shoulders (humpback), weakness of the limbs, unsteady gait, aortic stenosis, and premature aging. Psychologically, the individual may suffer confusion, depression, become argumentative with uncharacteristic explosive fits of anger, and contemplate suicide [4]. It is reasonable to suggest then that the drug also interferes with the amygdala-hippocampus emotional center of the brain [5].

Malignant cancers following long-term treatment with prednisone and prednisone-like immunosuppressant drugs have been reported [6–10]. This is the first report of multiple cancers following long-term treatment of TA with prednisone.

Case Report

On November 15, 2009, patient A.P. (female, age 74 years) presented at Dean Medical Ophthalmology Clinic, Madison, WI, USA, with symptoms of severe, unrelenting, temporal-region head pain and a drooping eyelid. A biopsy of the left temporal artery was performed at St. Mary's Hospital, Madison, WI, USA, and a diagnosis of giant cell arteritis with leukocyte infiltration was established together with Horner's syndrome [11]. The patient was placed on a regimen of 80 mg prednisone per day, which promptly relieved her symptoms. The strategy for control and treatment of TA for this patient was to monitor TA symptoms with

the inflammatory markers, C-reactive protein, and the erythrocyte sedimentation rate [12]. When symptoms were present or markers elevated, prednisone dosage was increased, and when decreased, prednisone dosage was decreased (Fig. 1). Lymphocyte data that appear in this history were part of emergency room diagnostic studies taken during her many admissions to the Emergency Department of St. Mary's Hospital. Before prednisone therapy and the onset of TA, the patient was an attractive, healthy, active elderly person. During prednisone treatment of her long illness, she experienced a bewildering array of severe drug side effects, including generalized disfiguring edema of the face, shoulders, legs, and ankles, several life-threatening infections, multiple cancers, and unusual behavioral changes that were foreign to her personality. A summary of her clinical history including lab tests, imaging results, clinical diagnoses, physical and personality changes, surgeries, and infections is given in Table 1 in the order of appearance after initiation of prednisone medication.

Figure 1 shows the quantitative data for prednisone dosage (mg/day), percent lymphocytes, and C-reactive protein on the ordinate and days following the beginning of treatment on the abscissa. Normal values for percent lymphocytes and the inflammatory marker, C-reactive protein, are given at the bottom of the figure. Erythrocyte sedimentation rates are not shown because these were consistently elevated throughout her illness and were not useful as a treatment marker, at least for this patients TA illness.

As seen in Figure 1, C-reactive protein was a reliable indicator of the TA status of A.P.'s autoimmune disease and a reliable prognostic marker for tracking the progress and treatment of her disease. When TA symptoms of temporal headache pain, polymyalgia rheumatic pain and other related symptoms were present, her C-reactive protein levels were elevated. When prednisone was given, her symptoms were promptly relieved and her C-reactive protein level was lowered to near normal values. Figure 1 also shows that prednisone not only controlled and relieved the inflammatory symptoms of TA, but also knocked down the patient's percent lymphocytes to dangerously low levels of 5% or less. Normal levels are between 17–25%. In effect, this decrease of lymphocytes severely compromised her natural cellular and humoral immunity to infection and cancer [3, 4, 6–10].

Table 1 gives the clinical history of A.P. over a period of nearly 6 years. During this time, the patient suffered from nearly constant disfiguring physical and painful signs of edema with swollen legs and ankles, moon face, and humpback shoulders. The symptoms were associated with unsteady gait and balance problems. Following surgery for removal of an adenocarcinoma of the right lower lung on day 360, during recovery on day 374, she experienced a pneumothorax in the same lung. On day 725 she was diagnosed with coronary atrophy and after that was constantly out of breath with general weakness and was unable to walk more than 100 feet even with assistance. She developed 3 serious infections, each requiring emergency room admissions and hospitalization. On day 440, she was diagnosed with bronchopneumonia and on day 864 she was treated for viral enteritis and septic shock with symptoms of severe vomiting and diarrhea. On day 1,230, she developed a urinary tract infection. For the duration of drug treatment, the patient developed a range of personality changes. She was often depressed, confused, disoriented, argumentative, and angry. She was given psychological counseling and during one private session asked the psychologist what drugs she could take to end her life. The patient died on February 10, 2016, with widespread multiple cancers of the colon and spinal cord.

This is the first time that multiple cancers of the lung, colon, and spinal cord have been reported following long-term prednisone treatment for TA. The data presented in Figure 1 and Table 1 support a view that multiple cancers in this individual developed as a consequence of long-term exposure to high doses of the immune knockout drug prednisone. During the 6 years of her illness, 4 of the 6 times her percent lymphocytes were counted, they were decreased far below normal levels and during the first year, 3 of the 4 blood tests gave percent lymphocyte counts of 5% or less. As a result, her natural immunity to infection and cancer were severely compromised, particularly during the first year when she developed lung cancer. In Figure 1 the down-pointing arrows indicate the day post-prednisone treatment when cancers were diagnosed. Surgery usually followed within days except for the soft tumor mass on L3 when the patient refused treatment and surgery. Note particularly that on day 104 following prednisone treatment, a benign 5-mm nodule diagnosed by imaging developed into an adenocarcinoma of the right lower lung at the same site 256 days later. On day 1,209 the patient was operated on for an adenocarcinoma of the distal transverse colon and 193 days later on day 1,402 underwent a colectomy for an adenocarcinoma of the ilium descending colon. Multiple, heterogeneous, synchronous, unrelated colorectal cancers have been previously reported in patients with inflammatory disease [13]. Again, as in the instance of the lung cancer, the ilium descending colon cancer was detected almost 1 year later. Two years later on February 10, 2016, day 2,212 following prednisone treatment, the patient finally succumbed after diagnosis of the soft tumor mass on lumbar vertebrae L3.

Discussion

The deleterious and disabling side effects of long-term, high-dose prednisone usage are well known, but reports have not emphasized how the side effects affect the lifestyle and overall wellness of the patient. In this case, the explosive and devastating side effects she endured when weighed against its benefits, begs for the discovery and development of targeted new drugs for the treatment of TA and other inflammatory and autoimmune diseases.

Regarding the unusual appearance of multiple cancers following long-term treatment with high doses of prednisone, it is unlikely that all 4 cancers at different sites and in different organ systems in 1 individual were caused by the spread of the primary lung tumor. Histologically the non-small cell lung cancer and cancers of the colon were diagnosed as adenocarcinomas. The soft tumor mass adjacent to caudal vertebrae L3 may have been a sarcoma, but since the patient refused surgery or treatment a biopsy was not performed. Staff pathologists were of the opinion that the appearance of multiple tumors in different organs in this patient in a relatively short period of time was an unusual outcome and provided no explanation. All pathology examinations were done at St. Mary's Hospital in Madison, WI, USA. Genomic sequence studies or immunological typing of the tumors were not performed, so the issue of relatedness could not be diagnostically resolved.

The argument for the appearance of multiple unrelated cancers in this patient comes from published reports on multiple unrelated cancers and routes of metastases. Tamura et al. [14], in a study of 729 cases of metastases in non-small-cell lung cancers, observed that

metastases were observed in bone, lung, brain, adrenal glands, liver, and extra-thoracic lymph nodes, but none metastasized to the colon or tumors of the caudal vertebrae. Also Naxerova et al. [15], in a similar study, reported that metastases of positive colon cancers follow the lymphatic routes to the liver and not the lung and when biopsies reveal nodes are cancer free, the risk of metastases to distant organs is less than 5% [16]. The draining lymph nodes of all 4 cancers of this patient were cancer free. These reports support the argument that the appearance of multiple tumors in this patient did not occur after metastases but were independent events.

Synchronous colonic multiple tumors in patients were studied by Cereda et al. [13]. In a study of 20 cases of genetically immunotyped synchronous colonic multiple tumors in patients with inflammatory diseases, they concluded that an environmental field effect, including the immune system, promotes multiple tumor formation in the background of inflammation which was the clinical situation with this patient.

To summarize, the development of multiple cancers in different organs of this patient did not correspond with published reports of routes of metastases from non-small cell lung cancer. The unusual clinical course of her metastatic illness while undergoing prednisone immunosuppressive therapy strongly suggests that the development of cancers were independent events and not the result of metastases from the original lung tumor.

The multiple cancers of this patient could have originated by two different mechanisms: (1) metastatic spread from any of the tumors or (2) developed after spontaneous independent mutations.

In either case, the absence of a functioning surveillance-immune system which is supported by her low lymphocyte counts would have permitted tumors from either one or both mechanisms to grow and thrive. Since tumor immunogenetic studies on this patient were not performed, the issue in her case is unresolved. However, since the patient was treated with high doses of prednisone during much of her illness, a favorable cellular immune environment existed that could have allowed multiple cancers to develop and thrive at the different organ sites.

In conclusion, it is reasonable to propose that in the absence of a functioning natural immune and surveillance system, spontaneous, multiple independent mutations occurred in several sites in the organ systems of this patient. Over a period of time, these mutations developed into malignant tumors, including the lung nodule which became cancerous 256 days later, as well as the cancers of the colon and soft tumor mass on L3.

Finally, the risk of cancer inductions in patients receiving long-term, high-dose prednisone therapy needs to be recognized and emphasized by medical practitioners as a consequence of this and other anti-inflammatory drugs. It is generally accepted that once a cell becomes malignant and develops into a solid tumor, particularly in a weak or malfunctioning immune system, it is usually resistant to any known clinical therapy other than surgery, chemotherapy, and radiation regardless of the person's subsequent immune status.

Recently, several novel strategies have been developed for the treatment of cancer: vaccinations using tumor-specific antigens attached to vaccinia and fowlpox viral carriers, and removing immuno-blocking checkpoints [17]. Genetically engineered CART cells that target tumor antigens have had some success against chronic and acute leukemias and prostate cancer. These treatments stimulate the release of cytokines by activated T cells, interleukins, and interferons that promote and coordinate the anti-tumor immune effects. Unfortunately,

these early trials sometimes have resulted in fatalities but are in the preliminary stages of development [18–21]. It is hoped that these new therapies will in time provide alternatives to steroid treatment.

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Statement of Ethics

Written informed consent was obtained from the patient's family.

Disclosure Statement

There are no conflicts of interests

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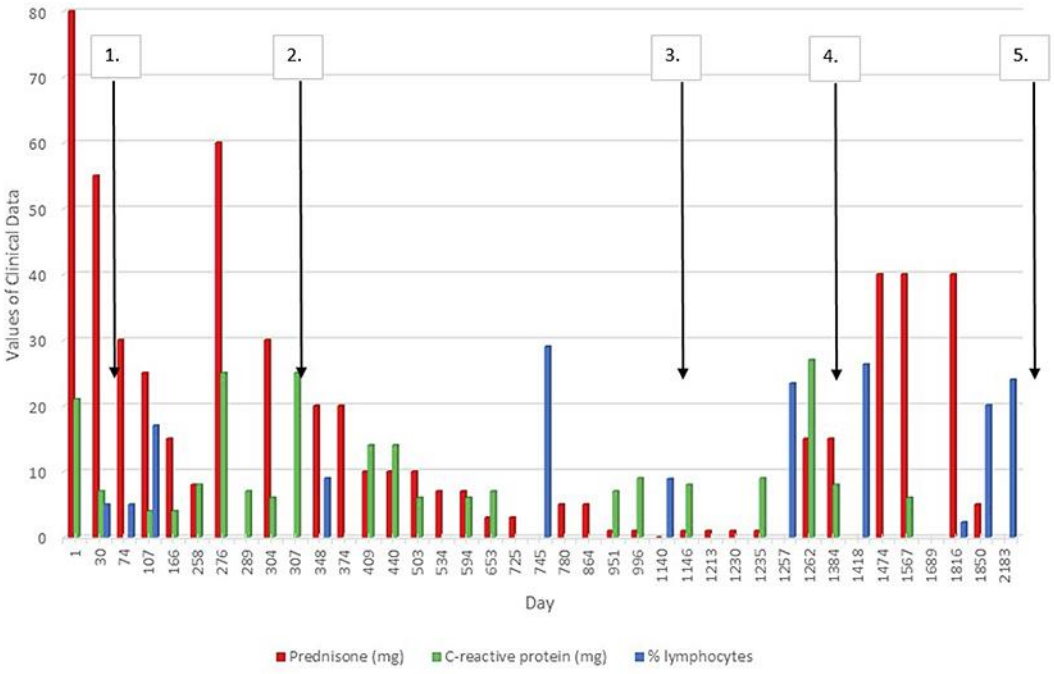

Fig. 1. The temporal relationships of prednisone dosage, response of lymphocytes, and C-reactive protein levels are presented as days after prednisone treatment (normal value of C-reactive protein, <5 mg; normal value of percent lymphocytes, 17–25%). Pre-malignant nodules, cancers, and surgery are given as numbers. The development of benign nodules and cancers are given as numbers above the graph: 1. Day 104 post-prednisone treatment (PPT) – 5-mm nodule, right lower lung. 2. Day 360 PPT – right lower lung adenocarcinoma. 3. Day 1,209 PPT – adenocarcinoma of distal transverse colon. 4. Day 1,402 PPT – adenocarcinoma of ilium descending colon, colectomy. 5. Day 2,212 PPT – soft tissue mass sarcoma of L3 vertebra.

Table 1. Clinical signs during prednisone treatment

Day PPT	Prednisone, mg	Symptoms and clinical signs
1	80	Severe headaches (temporal arteritis)
30	55	Severe leg pain, edema of legs, face, and shoulders
74	30	Edema of legs, face, and shoulders
107	25	*(Day 104 PPT – 5-mm nodule, right lower lung)* Edema of legs, face, and shoulders, unsteady gait, osteoporosis, COPD
166	15	Osteopenia, unsteady gait, COPD, edema of legs, face, and shoulders
258	8	Edema of legs, face, and shoulders, general weakness
276	60	Severe headache, edema of legs, temporal arteritis flare-up
304	30	Edema of legs, general weakness, unsteady gait
348	20	Edema of legs, general weakness, unsteady gait
374	20	*(Day 360 PPT – right lower lung adenocarcinoma)* Pneumothorax
409	10	Shortness of breath, general weakness, COPD, edema
440	10	Bronchopneumonia with fistula
534	7	Bilateral edema of limbs, unsteady gait, COPD
653	3	Bilateral edema of limbs, unsteady gait, general weakness
725	3	Syncope, coronary atrophy, memory and visual problems
780	5	Polymyalgia rheumatica, osteopenia
864	5	Sepsis, vomiting, diarrhea, severe hypotension, shock, and acidosis
951	1	Aortic stenosis
1,140	0	Vomiting, diarrhea, viral enteritis, eye pain
1,213	1	*(Day 1,209 PPT – adenocarcinoma of distal transverse colon)* General weakness, shortness of breath, COPD
1,230	1	Urinary tract infection
1,262	15	Lower bilateral leg pain
1,474	40	*(Day 1,402 PPT – adenocarcinoma of ilium descending colon, colectomy)* Non-productive cough, fatigue, shortness of breath, temporal arteritis, large artery involvement, right lower lobe pneumonia
2,208	Not taken	Soft tumor mass sarcoma on L3 lumbar vertebrae with kidney involvement, severe bilateral back pain
2,221		*(Day 2,212 PPT – soft tissue mass sarcoma of L3 vertebra)* Patient expired (February 10, 2016)

PPT, post-prednisone treatment.