Coley's toxin: Historical Perspective

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Key words: Coley's toxin, soft tissue sarcoma, erysipelas, *Serratia marcescens*

IMAJ 2002;4:471–472

The fact that an acute bacterial infection can induce a regression in a concurrent malignant tumor has been known for hundreds of years. However, only in 1868 – when Busch intentionally infected a patient with a soft tissue sarcoma of the neck with erysipelas, hoping that it will cause a tumor regression – was it implemented. Since the causative agent of erysipelas was not known at that time, the patient was placed in a hospital bed notoriously known for the frequency with which patients in it became infected with erysipelas. After being infected with erysipelas, rapid tumor shrinkage was observed [1]. This response was only partial and tumor recurrence subsequently occurred [1]. Only 13 years later, in 1881, was *Streptococcus* identified as the causative agent of erysipelas.

In 1891, Dr. William B. Coley, a New York surgeon just beginning his career, treated a young patient with a soft tissue sarcoma of the arm. Although a radical excision of the tumor was performed, the patient developed metastatic disease and died. Frustrated by the inability of surgery to achieve cure and being unaware of Busch's work, Dr. Coley searched the medical records of the hospital and located a 7 year old record of a patient with an inoperable sarcoma that persistently recurred after repeated resection attempts. That patient ultimately became infected with erysipelas. Following the patient's recovery from that infection, a regression of the malignancy was documented. Coley located the patient and found him to be free of disease. Stunned by that finding, he further searched the medical literature and found a substantial number of publications documenting the same observation; namely, that a concurrent infection may lead to regression, and even cure, of an underlying malignancy.

Coley speculated that the infection around the tumor site induced a direct cytotoxic reaction, and in May 1891 he conducted the first treatment of an inoperable tumor with local injections of streptococcal cultures. His patient had an extensive lymphoma of the neck that recurred after two excisions and caused severe difficulty in swallowing, weight loss, and cachexia. Injections of streptococci were given to the patient at 3–4 day intervals over a few weeks. Following a severe attack of erysipelas, the tumor underwent extensive necrosis and the patient remained disease-free for 8 years [2]. Encouraged by this outcome, Coley used injections of streptococci to treat other patients with a variety of malignant tumors. The clinical results were variable. The rate and extent of response differed from patient to patient; in some the rate of tumor response was rapid and in some very slow. It was attributed to the different tumor types in that series of patients but also to differences in the severity of infection among these patients. Coley noticed a clear correlation between the severity of patients' response to the injection and the tumor response. On the basis of other observations that the presence of *Serratia marcescens* can enhance the virulence of streptococci, Coley incorporated that bacterium into the streptococcal vaccine. It was the combined injection of these two heat-killed bacteria that would eventually be referred to as "Coley's toxin." [3].

Coley noted that even an injection in a remote anatomic site could result in impressive tumor response. This phenomenon, combined with his previous finding that tumor response was related to the severity of infection, led him to conclude that the infection evoked a systemic response, the nature of which was unclear at that time, and resulted in tumor destruction.

Administration of the toxin was a complex procedure that when performed inadequately may result in significant morbidity and even mortality. Most patients were injected every other day for a few weeks. Special attention had to be given to the dose of the toxin, the site and depth of injection, frequency of injections, and length of treatment. The intravenous route was found to be the most effective, and a dose of the toxin was considered sufficient only when its injection was accompanied by high fever. The aim was to produce a rise of temperature to 40–40.5°C accompanied by a chill [4,5].

Over the next 45 years, until the end of Coley's medical career in 1936, thousands of patients were treated with Coley's toxin. Coley gained extensive experience in the treatment of a large variety of malignant diseases, including soft tissue sarcomas, lymphomas, osteosarcomas, Ewing's sarcomas, and malignant melanomas. He also treated cervical, ovarian, testicular, renal, breast, and colorectal carcinomas. The best response by far was achieved in patients with inoperable soft tissue sarcomas; long-term (more than 5 years) disease-free survival was achieved in approximately 50% of these patients. Carcinomas, on the other hand, responded poorly to the treatment, and Coley concluded that the use of the toxin should be limited to sarcomas.

Coley's fascinating observations and vast clinical experience led to the understanding that the immunologic host response may influence the biologic behavior of some malignant tumors, and that

manipulation of that balance might therefore result in recognition of the tumor by the immune system, initiation of immune response, and tumor kill. Activation of the immune system, either by making it respond to an iatrogenic infection as Coley did, or by treating the patient with a cytokine that is part of the immune cascade (i.e., interleukin-2, interferon, or tumor necrosis factor), is the principle underlying contemporary cancer immunotherapy. Coley's toxin has been cited as a promising treatment that may have been prematurely abandoned with the advent of modern chemotherapy, radiotherapy, and improvement in surgical techniques.

References

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