The Journal of Laryngology & Otology (2015), ***129***, *1248–1250.*

doi:10.1017/S0022215115002595

CLINICAL RECORD

Spontaneous regression of laryngeal squamous cell carcinoma

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Abstract

Background: Spontaneous regression of solid malignancy is extremely rare. It is virtually unheard of in the last half century in the published literature. The overwhelming majority of medical professionals do not know that this phenomenon exists.

Case report: This paper reports such a case involving a patient with proven laryngeal squamous cell carcinoma in New Zealand. Whilst waiting for definitive treatment, he was afflicted with prolonged septicaemia secondary to peritonitis from percutaneous endoscopic gastrostomy tube insertion. Following a total laryngectomy, histology of the specimen did not contain any evidence of neoplasia.

Conclusion: Based predominantly on work established by Dr William Coley, we believe that a period of prolonged pyrexia preceding definitive surgery contributed to this apparent 'miracle'. The time may be ripe to further debate on whether the medical profession should consider pyrexia therapy as a last resort treatment for patients deemed incurable by conventional methods.

Key words: Spontaneous Neoplasm Regression; Larynx; Squamous Cell Carcinoma; Pyrexia; Immunotherapy

Introduction

Spontaneous regression of cancer is virtually unheard of in the modern era of medicine. A confirmed case of laryngeal cancer in New Zealand which disappeared completely in the laryngectomy specimen raises the question whether this phenomenon does exist. We performed a literature search of the PubMed database using combinations of relevant article title words in an attempt to provide possible explanations for these rare events.

Case report

A 66-year-old male, who was a long-standing smoker, was seen in an otolaryngology clinic on 5th May 2006. His only complaint was of two months' hoarseness. There was no significant past medical history. Flexible nasendoscopy revealed leukoplakia involving the anterior to middle portion of the left vocal fold.

Microlaryngoscopy was performed on 22nd June. Histology of the left vocal fold showed moderately differentiated squamous cell carcinoma (SCC) (Figure 1). The patient was referred to a head and neck surgeon at a tertiary level hospital.

The tumour was graded as T_3 on 17th July, as the left vocal fold was fixed on flexible nasendoscopy. A computed tomography (CT) scan supported the tumour–node–metastasis staging of $T_3N_0M_0$ for the left glottic SCC. The curative options available were either a total laryngectomy, with or without post-operative radiotherapy, or chemoradiotherapy. Following a multidisciplinary team meeting, the patient was scheduled for chemoradiotherapy.

Unfortunately, the patient was admitted with significant percutaneous endoscopic gastrostomy tube site cellulitis following insertion on 7th September. Gastric content was leaking around the percutaneous endoscopic gastrostomy tube with concomitant severe abdominal pain, which necessitated tube removal. There was substantial gastric ulceration at the former tube site. The fistula continued to drain greater than 1 litre per 24 hours for some days. A CT scan identified multiple intra-abdominal collections. These were drained under ultrasound guidance and the drains were left in situ for several days. The patient was also given intravenous antibiotics and fed via a nasojejunal tube. As indicated in Figure 2, he was markedly unwell, with a prolonged period of raised inflammatory markers. Based on available records (Figure 3), he had swinging pyrexia for at least 14 days. He recovered sufficiently after five weeks and was discharged on 4th November.

Because of the prolonged illness, the patient was deemed unfit for chemoradiotherapy. A repeat CT scan of the neck and chest in September showed increased thickening of the left vocal fold posteriorly around the arytenoid region. There was no evidence of regional or distal metastases. Repeat microlaryngoscopy (with no repeat biopsy) was performed on 17th October to reassess the tumour. As radiotherapy alone was less likely to cure the patient, he was counselled and scheduled for a total laryngectomy.

Despite clinicians' strong advice, the patient delayed surgery for several months, until April 2007. Amazingly, detailed histological examination of the total laryngectomy specimen revealed no evidence of carcinoma. There was

Accepted for publication 16 June 2015 First published online 7 October 2015

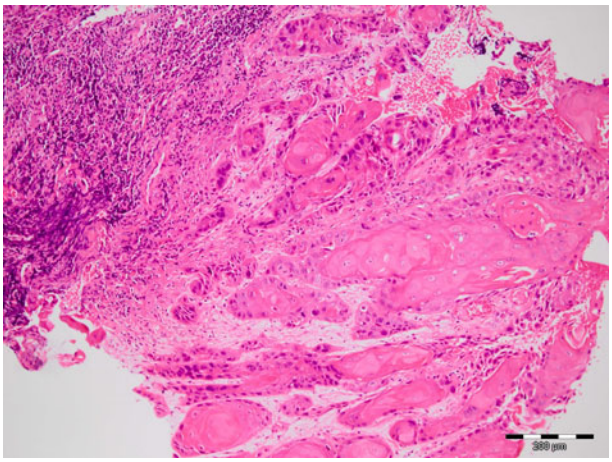

FIG. 1

Histology slide from vocal fold. The epithelium shows considerable atypia and buds of atypical squamous epithelium infiltrate downwards into the subjacent connective tissues. These show focal keratinisation. This is moderately differentiated squamous cell carcinoma. (H&E; ×100)

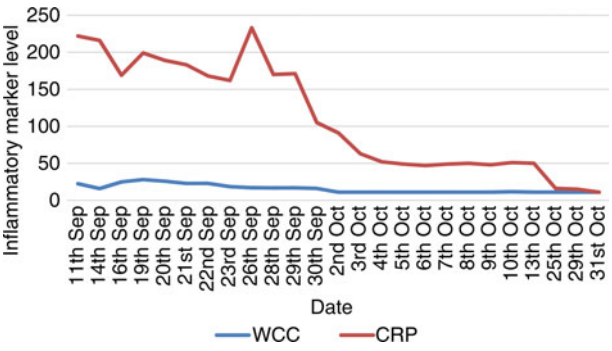

FIG. 2

Graph showing fluctuating raised inflammatory markers. Sep = September; Oct = October; CRP = C-reactive protein (normal value, <5 mg/l); WCC = white cell count (normal range, 4–11 × 10^9/l)

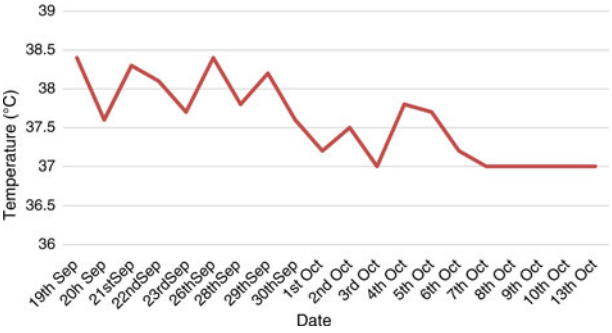

FIG. 3

Graph showing fluctuating pyrexia over a period of about three weeks. Average normal temperature was taken to be 37 °C. Sep = September; Oct = October

only moderate dysplasia visible on serial sections. The pathologists in the hospital where the laryngectomy was performed naturally revisited the microlaryngoscopy biopsies conducted in the first hospital and concurred with the original diagnosis of moderately differentiated glottic SCC. Therefore, there is absolutely no doubt that the patient did have laryngeal SCC on presentation.

As of September 2013, the patient was still alive, with no sign of tumour recurrence.

Discussion

Everson and Cole defined spontaneous regression of cancer as the partial or complete disappearance of a malignant tumour in the absence of all treatment or in the presence of inadequate treatment.[1] This is an extremely rare phenomenon. There are no actual figures, only estimates of its incidence. These vary from 1:80 000 to 1:100 000 cases of cancers.[2] In a review covering the period 1900 to 1956, Everson and Cole found only 1 case of spontaneous regression of laryngeal cancer out of a total of 176.[1] Challis and Stam verified 4 cases of laryngeal cancer with spontaneous regression from a total of 504 during the period 1966 to 1987.[2]

To our knowledge, this is only the seventh report in the published literature of a laryngeal cancer demonstrating spontaneous regression. It is the only report in the last 45 years, since a report of spontaneous regression of laryngeal SCC following microlaryngoscopy and biopsy only.[3]

There have been attempts to explain these cases, with theories including immunological or endocrine factors, surgical necrosis, infection, or operative trauma factors,[2] but the most compelling explanation is immune system activation by infection, as demonstrated by William Coley.

Dr William Coley (1862–1936) believed that with the right kind of stimulation, the body could rid itself of cancer cells.[4] He was an orthopaedic surgeon dealing with bone malignancies. Following a very personal experience managing a 17-year-old female patient with osteosarcoma in her metacarpal, who died despite forearm amputation, Coley vowed to find a way of helping similar patients.[4]

Coley searched through previous reports of spontaneous regression of cancers and discovered that a common theme was that most of those patients had prior erysipelas with pyrexia. He took this idea forward and developed his own method of inciting fever in selected patients. His first patient was injected in 1891 with live streptococcal organisms to establish erysipelas, which induced pyrexia and was thought to stimulate the immune system. Two out of three of his first cohort of patients died of infection. The patient who recovered from the erysipelas also survived the malignancy. It became apparent that it was safer to use killed organisms, and Coley concluded that a combination of *Streptococcus pyogenes* and *Serratia marcescens* (formerly *Bacillus prodigiosus*) was best, based on research at that time. The latter bacteria were believed to increase the virulence of the former.[5] This concoction was later called Coley's toxin.

The initial response by the medical community was severe criticism and complete dismissal. This was not wholly unexpected as Coley's methods of treatment and follow up results were inconsistent. There were at least 13 different versions of Coley's toxin, with some of them commercially manufactured. The American Medical Association rejected his work in 1894, but later reversed their position in a 1934 *Journal of American Medical Association* editorial. Subsequent review of his work by his daughter indicated that he cured some of those patients who otherwise would have perished.[6]

https://doi.org/10.1017/S0022215115002595 Published online by Cambridge University Press

Fever is accompanied by diverse immunological changes, such as increased biochemical reaction rates, and enhanced leucocyte proliferation, maturation and activation. Febrile thermogenesis is a metabolically expensive process; metabolic rates increase two to three times, whilst fever maintenance has been associated with a 30–50 per cent rise. Thus, it is unlikely that such a response would be physiologically conserved in humans and some animals unless it had a considerable adaptive value. Any immune response to pathogens giving rise to fever is associated with a multitude of cytokine cascades, which then triggers other cascades and a diversity of cellular responses.

This immune cascade was readily evoked through the use of Coley's toxin, but virtually impossible to reproduce with single cytokine therapy. It was initially reported that Coley's toxin only worked for sarcomas, but it was later shown to be effective against carcinomas, lymphomas, melanomas and myelomas.[5] With the establishment of radiotherapy and then chemotherapy as the non-surgical workhorses of cancer management, Coley's work became less and less known, especially by younger generations of physicians. To these doctors, cancer is an irreversible process with no physiological cure.

- **Spontaneous regression of solid cancer is virtually unheard of in the modern medical era**
- **The most likely explanation is physiological immunotherapy secondary to the body's response to prolonged pyrexia, as demonstrated by Dr William Coley**
- **This paper reports such a case in a laryngeal squamous cell carcinoma patient**
- **The patient developed septicaemia before undergoing radical surgery, with subsequent histology showing no evidence of cancer**
- **Immunotherapy is increasingly recognised to play a major role in some cancers**

This case is remarkable for at least two reasons. The most significant event was the prolonged infection secondary to peritonitis as a consequence of leakage from percutaneous endoscopic gastrostomy tube insertion. This gave rise to intermittent but prolonged pyrexia. The second was the length of delay in performing surgery. The patient was diagnosed in June 2006 and only underwent laryngectomy in April 2007, which is a considerable delay of about 10 months.

Conclusion

In the last half century, the accepted therapies for cancer are surgery, radiotherapy, chemotherapy or a combination of these. It has become increasingly apparent that immunotherapy may have a significant role (i.e. human epidermal growth factor receptor 2 positive breast cancer treated with Herceptin® and BRAF-positive melanoma treated with vemurafenib).

Coley is widely regarded as the father of cancer immunotherapy.[4] He might not have identified the exact immunological mechanism, but he activated the body's own powerful immune defences to eradicate cancer cells. Based on his work, the most likely explanation for the spontaneous regression in this case was the epic immunological response triggered by infection leading to pyrexia.

With this as a possibility, perhaps, following a life-threatening episode such as septicaemia in a cancer patient, a repeat biopsy might be warranted. However, it would have been a courageous surgeon who would not have proceeded to radical surgery in this case. A negative repeat biopsy in this patient would have led to further biopsies for fear of false-negative results. As long as there are visible and radiological abnormalities, these biopsies would have been repeated again and again, which could result in further delay and significant morbidity. We believe, as did Hoption Cann *et al.*,[5] that case reports such as this illustrate the need to revisit Coley's work and to formulate a standard of pyrexia immunotherapy. This treatment regime could be considered in selected patients for whom all other conventional therapies are considered futile.

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Mr F Sipaul takes responsibility for the integrity of the content of the paper
Competing interests: None declared

https://doi.org/10.1017/S0022215115002595 Published online by Cambridge University Press