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Case Report
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# Phlegmon Formation as an Unforeseen Complication Following Radiotherapy of the Hypopharynx

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## Abstract

Phlegmon is an extremely rare and usually unforeseen complication in patients with malignant neoplasms, who undergo radiotherapy. The condition is usually of a bacterial origin and its formation may be precipitated by an impaired immune system. In this case report, we present a 54-year-old male who has undergone radiotherapy treatment for squamous cell carcinoma in the tonsil-lingual angle. Four months later, the patient developed radionecrosis with subsequent edema, bleeding, epithelial changes, as well as signs of acute infection that rapidly spread from neck to chest and the stomach. Ultimately, the patient has been diagnosed with radionecrosis and phlegmon complicated by radiotherapy and poor health status. Our primary interest was to investigate why the patient has developed a phlegmon, as this is a very atypical consequence following radiotherapy. We refer to the literature to determine if a similar case has been reported in the head and neck area. We suspect that the etiology related to the radiation therapy is complicated by the patient's compromised immune system.

**Keywords: Radionecrosis; Phlegmon; Oncology**

## Abbreviations

IMRT: Intensity-Modulated Radiotherapy; SCC: Squamous Cell Carcinoma; PEG: Percutaneous Endoscopic Gastrostomy; DMT2: Diabetes Mellitus Type 2; CT: Computerized Tomography; NPWT: Negative Pressure Wound Therapy; VAC: Vacuum Assisted Closure

## Introduction

Phlegmon is a diffuse, acute suppurative inflammatory process affecting the subcutaneous connective tissue. It typically occurs in response to bacterial infection. If the infection is not managed, it can spread and become life-threatening. The patient that we present in this case report has completed radiotherapy targeted at the hypopharynx. Four months later, he developed soft tissue necrosis in the site of the tumor and a diffuse phlegmon that spread from the neck to the chest and stomach. The development of a phlegmon under these circumstances is very atypical. To the best of our knowledge, this is the first case reporting phlegmon as an adverse effect of radiotherapy. The aim of this report is to investigate the potential causes of phlegmon development following radiation therapy. We consider several factors such as the presence of radionecrosis, the effect of radiotherapy, as well as immune system function.

## Case Presentation

In September 2019 a 54-year-old Caucasian male presented to the otolaryngology department for a biopsy of the tonsil-lingual angle due to the suspicion of a recurrent tumor. The patient has a history of SCC of the hypopharynx, which was treated by radiotherapy. The biopsy results showed no malignant changes; however there was evidence of radionecrosis.

The radiated tissue was edematous and foul-smelling, the mucosal epithelium was dry, rough, friable with a change in color, and significant bleeding was noted. Two weeks after the biopsy was taken, the patient returned to the hospital with swelling on the right side of the neck, dyspnea, and dysphagia. A microbiological swab was taken from the oral cavity at the biopsy site. The culture was positive for *E. coli* and *C. albicans*. Clindamycin and metronidazole were prescribed. The patient was admitted to the hospital for a month until the end of October 2019 for further investigation and treatment. The patient had a medical history of similar edema of the neck after radiotherapy, which improved after systemic steroids.

On October 1, another microbiological swab was taken; this time from the patient's neck.

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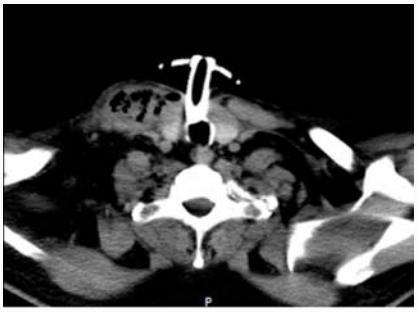

**Figure 1:** Axial CT image of the neck. Visible asymmetry on both sides of the tracheostomy tube and areas of radiolucency on the right side, which are indicative of inflammation. Phlegmon infiltrates the right sternocleidomastoid muscle.

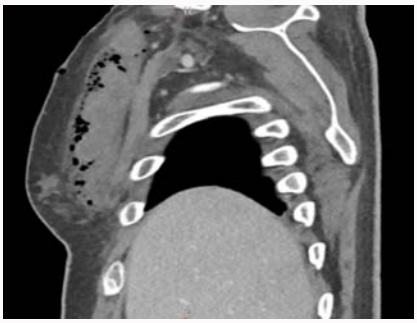

**Figure 2:** Sagittal CT image of the thorax. Visible inflammation and edema in the anterior chest wall indicative of phlegmon. Bubbles of air in the soft tissues of chest are suggestive of anaerobic inflammation.

This culture tested positive for *C. glabrata* and nystatin was administered locally. Additionally, fluconazole and tazocin were added intravenously. Two weeks later, another neck swab was performed as there was no improvement in the patient. The culture tested positive for *E. coli*, *K. oxytoca*, *C. albicans*, *Acinetobacter* sp., and *S. haemolyticus*. Fluconazole administration was continued and trimethoprim/sulfamethoxazole was added.

The patient was diagnosed with SCC of the right tonsil-lingual angle in December 2018. In preparation for radiotherapy, the patient underwent a tracheotomy and PEG in February 2019. IMRT with 70Gy lasted for six weeks and treatment was completed in May. In addition, the patient's medical history shows that he suffers from DMT2 and hypertension. Furthermore, he is HPV positive. The patient also smokes and drinks occasionally. His routine medications include atorvastatin, metformin, diclofenac, silibinin, and dexamethasone. Fentanyl was prescribed for pain relief. Since the patient was put on an enteral feeding regimen during hospitalization, metformin was replaced with actrapid, human soluble insulin.

Several laboratory and imaging tests were performed during hospitalization. The most significant parameters were C-Reactive Protein (CRP), Procalcitonin (PCT), and blood glucose levels. Upon admission, CRP and PCT values were very high; laboratory results recorded the patient's CRP level to be 420.1 mg/L and PCT was 2.38 ng/mL, indicating that the patient had significant inflammation and was septic. Furthermore, blood glucose levels were uncontrolled because they were consistently high and variable. Blood glucose levels ranged from 100 mg/dL to 337 mg/dL, with an average value of 186.8 mg/dL. Additionally, CT results showed inflammation and edema of the neck, chest, and stomach (Figures 1-3). Incision and drainage

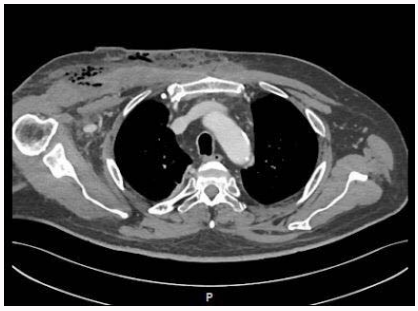

**Figure 3:** Axial CT image of the thorax. Conspicuous right-sided edema that causes chest wall asymmetry.

were performed at each site of the body where there was a reservoir of pus. This procedure was repeated three times. VAC with NPWT was initiated with positive improvements. The patient was diagnosed with a phlegmon with a suspected etiology related to radionecrosis.

## Discussion

Edema of the laryngeal mucosa is a common finding following radiotherapy for laryngeal cancer, usually subsiding within 4 to 6 weeks. However, edema that persists months after the completion of radiotherapy may induce an inflammatory state, indicating a more severe process, namely incipient necrosis or recurrent malignancy. This alteration may be due to: (i) Uncontrolled infection, (ii) susceptibility of irradiated tissue to infection, (iii) excessive radiation dosage in comparison to the patient's tolerance and susceptibility to infection, as well as (iv) impaired tissue resistance due to diabetes [1].

Furthermore, the biopsy site may act as an entryway for infection, but also trauma in the area may cause vascular damage, ulceration, and radionecrosis [1]. However, the post-irradiation biopsy was not the cause of phlegmon development and necrosis in the current patient for three reasons. First, upon clinical examination on the day of the biopsy, the radiated tissue was already edematous with significant oral epithelial changes. Second, the biopsy results showed evidence of tissue necrosis; therefore, necrosis was already present prior to the biopsy visit. Finally, sterilization issues can be omitted, as no additional patient developed an infection during that shift, nor did they have similar symptoms as our patient.

The literature reports several accounts of brain abscess formation and temporal lobe necrosis following radiation therapy for Nasopharyngeal Cancer (NPC). Cheng et al. hypothesize that radiation necrosis tissue is responsible for acute infection progression [2]. The research based on animal study models shows that necrosis of small blood vessels causing progressive ischemia and necrosis of the brain may facilitate the formation of this acute infection rather than direct or indirect exposure of bacteria. Also, local infections further increase the risk of developing a brain abscess, particularly nasal or ear infections, and may act as predisposing factors [2]. In this report, necrotic tissue formed as a complication of radiotherapy, could be the facilitating element triggering an acute infection. This in combination with the patient's compromised immune system, due to uncontrolled diabetes, could increase the risk of developing an acute infection.

Fraction size during radiotherapy is of significant importance. Studies show that external beam radiation doses more than 72Gy in NPC patients, resulted in a greater incidence of temporal lobe necrosis than patients who were administered a lower dose [3]. Furthermore, radiation-induced necrosis in NPC patients occurred more often

during the treatment with conventional 2D radiotherapy than with 3D or IMRT treatment. IMRT is advantageous because radiation is delivered to the site of the tumor, protecting the surrounding tissues. It also requires a lower maximal dose compared to 2D radiotherapy. It is recommended to re-evaluate the patient's IMRT treatment before the 25$^{th}$ fraction to ensure that the patient is receiving the adequate dose [3].

While there is a strong correlation between radiotherapy and tissue necrosis, radiotherapy also contributes to depression of cell-mediated immunity. There has been evidence that lymphopenia and decreased lymphocyte stimulation with Phytohaemagglutinin P (PHA-P) sometimes follow irradiation in evaluated bladder carcinoma patients and generally in cases where high doses of radiation are administered to anatomical sites [4]. The exact mechanism of immunosuppression in such cases is controversial, but mostly it is attributed to irradiating large volumes of blood in the treatment field [5].

Furthermore, the immune system impairment may be caused by uncontrolled blood glucose levels. As mentioned earlier due to the necessity of enteral feeding regimen the administration of actrapid substituted metformin which had been taken by the patient regularly prior to hospitalization. Nevertheless, the patient's blood glucose levels were still uncontrollably high, which may have been attributed to the stress hyperglycemia that often accompanies sepsis. The mechanisms that explain these findings are (i) general metabolic shift towards catabolism; (ii) impaired insulin sensitivity and disrupted balance between insulin and its counter-regulatory hormones (glucagon, cortisol, growth hormone, and catecholamines) in peripheral tissues that results in increased availability of amino acids and free fatty acids arising from a shift towards proteolysis and lipolysis; (iii) non-pulsatile and insufficient secretion of insulin in the chronic phase of sepsis; (iv) an increase in ACTH secondary to a rise in corticotropin-releasing hormone and inflammatory mediators like TNF-alpha which leads to increased secretion of cortisol and increases blood levels of glucose, amino acids, and free fatty acids; (v) increased levels of endogenous catecholamines that result in increased hepatic gluconeogenesis and inhibit Insulin-Mediated Glucose Uptake (IMGU) by induction of insulin resistance. Therefore, management of hyperglycemia during hospitalization of our patient has been challenging not only because of DMT2, but also due to drastic metabolic alterations seen in sepsis [6]. Dexamethasone may have also been a factor that contributed to the partial suppression of the immune system.

The scientific data demonstrates that hyperglycemia causes a deficiency of C4 component of the complement system, decreased secretion of IL-1 and IL-6 by mononuclear cells and monocytes in response to stimulation by lipopolysaccharides as a consequence of an intrinsic cellular defect, as well as decreased mobilization of polymorphonuclear leukocytes, chemotaxis, and phagocytic activity. Moreover, Glucose-6-Phosphate Dehydrogenase (G6PD) is undermined by a hyperglycemic environment and thus apoptosis of polymorphonuclear leukocytes is increased and their transmigration through endothelium is decreased [7].

Owing to the fact that the predisposing factors for the development of phlegmon in this case report are multiple and rather diverse, it is difficult to predict the exact etiology for its development. Factors including persistent edema following radiotherapy, biopsy complications, presence of necrotic tissue, and radiotherapy fraction size are plausible explanations for phlegmon development, however, we believe the patient's impaired immune system was the leading cause that contributed to this widespread acute infection.

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