ABSTRACT

Objectives

Anecdotal evidence suggests that oropharyngeal squamous cell carcinoma (OPSCC) should be suspected in patients presenting with symptoms of peritonsillar abscess (PTA) or cellulitis (PTC). The aim of this study was to estimate the prevalence of OPSCC in patients presenting with symptoms of PTA/PTC.

Method, Setting and Participants

We retrospectively identified all adults with a coded diagnosis of PTA or PTC who presented between 2012-2016 inclusive, across six ENT units in Merseyside. Records were compared to that of the centralised regional head and neck cancer database. The clinical records of a subset of patients were reviewed for the purposes of data validation.

Results

A total of 1975 patients with PTA/PTC were identified. Three patients were subsequently diagnosed with OPSCC. None of the three actually had an objective underlying diagnosis of PTA/PTC on the same side. The prevalence of OPSCC in patients admitted with symptoms of PTA/PTC was 0.15%, or approximately 1:650 admissions. The records of 510 patients who presented over a one-year period (2016) were reviewed in even greater detail. There were 298 patients with PTA (59.4%), 151 with PTC (29.1%) and 61 had an alternative diagnosis (11.9%). High risk features (age ≥40, tonsillar asymmetry or tonsillar lesion) were present in 106 patients (24%). Urgent follow up was expedited for 77 patients (73%).

Conclusion

This study estimates the risk of OPSCC in patients with peritonsillar symptoms. The prevalence is low, even in a region with a relatively heavy disease burden. Clinicians should, however, retain a high level of suspicion in patients with persistent symptoms.

KEY POINTS

- Anecdotal evidence suggests that oropharyngeal squamous cell carcinoma (OPSCC) can present as peritonsillar abscess (PTA) or peritonsillar cellulitis (PTC).
- In this study, the prevalence of OPSCC was 3:1975 patients in a five-year period, or 0.15%. Approximately 1:650 patients who presented acutely with symptoms of PTA/PTC had an underlying OPSCC. No cancer patient had objective evidence of PTA.
- Approximately 1% of patients (3 of 292) diagnosed with tonsillar SCC in the same period presented as an emergency with symptoms of PTA/PTC.
- Clinicians should have a high index of suspicion for cancer in patients presenting acutely with unilateral sore throat refractory to treatment with antibiotics.
- Higher risk features include age ≥40 years, the presence of tonsillar asymmetry or a focal tonsillar lesion, and a significant alcohol and smoking history.

INTRODUCTION

Oropharyngeal squamous cell cancer (OPSCC) is the second most common mucosal malignancy of the head and neck. Incidence has been steadily increasing for several decades and this is partly attributed to human papillomavirus (HPV) [1].

While patients with HPV-positive OPSCC tend to have a better prognosis [2], early diagnosis and prompt treatment are essential for improved survival and quality of life. The most common presenting symptoms of OPSCC are neck mass (44%), sore throat (33%) and dysphagia (16%) [3]. There are, however, sporadic case reports in the literature of patients presenting initially with symptoms of peritonsillar abscess (PTA) or cellulitis (PTC), who are subsequently found to have an underlying OPSCC [4,5].

Perhaps based on this knowledge, many otolaryngologists teach that clinicians should be wary of cancer in the older patient presenting with unilateral symptoms similar to PTA/PTC. Moreover, there is uncertainty within this 'oral tradition' as to whether it is a case of patients with OPSCC presenting with symptoms mimicking PTA, or whether it is a case of an objective, aspirate-proven PTA caused by an OPSCC.

Given this anecdotal knowledge, many otolaryngologists follow up patients with high-risk features once initial infection had resolved. High-risk features are thought to include increasing age (variable cut-off; ≥40 years in many units), unilateral tonsillar lesion or tonsillar asymmetry, and a history of significant exposure to smoking or alcohol.

A literature search identified no large studies on the subject. Since PTA is a relatively common ENT emergency, being able to stratify the risk of cancer could help to rationalise services and inform both clinicians and patients.

Objectives

We sought to determine the approximate prevalence of OPSCC in patients who had presented with symptoms of PTA/PTC. We also wanted to audit current follow-up practices against a putative guideline using some of the risk factors mentioned above.

METHODS

Ethical considerations and governance protocols

Using the Health Research Authority online tool (http://www.hra-decisiontools.org.uk/research/), this study was not considered to represent research. The study was registered as a service evaluation with the appropriate clinical governance authority at each site: [redacted] (lead); [redacted]; [redacted]; [redacted]; [redacted]; [redacted]. We followed applicable information governance protocols and sought relevant permissions at each site before sending pseudo-anonymised records to the lead site for secure collation. To protect patient confidentiality, we decided that we would not report any patient-specific details if we identified fewer than ten patients with OPSCC.

Reporting guideline

The STROBE guideline has been used in the preparation of this manuscript.

Study design and setting

This was a retrospective multicentre observational study based in secondary care.

Participants and data sources

We retrospectively identified patients who presented to all six sites who had a coded diagnosis of PTA or PTC (International Classification of Diseases-10 (ICD-10) code J36) over a five-year period between 1 January 2012 and 31 December 2016 inclusive. Since head and neck oncology services are centralised in Merseyside, we compared data on all those with a coded diagnosis of PTA/PTC to diagnoses of OPSCC held in the regional head and neck cancer database. The comparison group from the cancer database extended 24 months beyond the end of the PTA/PTC study period to allow for diagnostic and other delays.

Sample size

Anecdotally, a diagnosis of OPSCC is rare in this context, so we wanted to capture a large number of cases of PTA/PTC (between 1500 and 2000). We based the sample period on previous audit data that showed approximately 1-2 admissions for PTA/PTC per week in a

district general hospital ENT department; we projected that a five-year period might yield approximately 2000 cases of PTA/PTC across our region.

Exclusion criteria

We excluded individuals under the age of 16 and whose who had a coded diagnosis of tonsillitis (ICD-10 J03), chronic tonsillitis (ICD-10 J35), parapharyngeal abscess (ICD-10 J39) or retropharyngeal abscess (ICD-10 J39).

Study end-points

The primary end-point was the number of patients with a diagnosis of OPSCC within 24 months of a coded diagnosis of PTA/PTC. We reviewed the records of any patients who had both a coded diagnosis of PTA/PTC and OPSCC, for verification purposes. As well as demographic data, we captured time to OPSCC diagnosis, anatomical subsite, age, sex, smoking and alcohol history and TNM stage.

Validation cohort

We reviewed the medical records of all patients presenting during a one-year period (1 Jan 2016 to 31 December 2016 inclusive). Coding accuracy was verified to reduce the chance of bias. Given the risk factors set out above (age ≥40 years; focal tonsillar abnormality; tonsillar asymmetry), we also audited the number of patients who would have been followed up should those risk factors have formed the basis of a guideline. We did not include smoking status in this analysis as this was universally poorly recorded across all six study sites.

RESULTS

Prevalence of OPSCC in patients with a coded diagnosis of PTA/PTC

A total of 2244 inpatients were initially found to have a coded diagnosis of PTA during the study period. We excluded 269 cases to account for clinical coding accuracy, bringing the total down to 1975. Three of these patients were subsequently diagnosed with a squamous cell carcinoma (SCC) of the upper aerodigestive tract. All three were OPSCC centred on the tonsil.

The prevalence of OPSCC was therefore 3:1975 patients over five years, or 0.15%. In this study, approximately 1:650 patients who presented acutely with symptoms of PTA/PTC had an underlying OPSCC.

Looking at the data from a cancer point of view, there were 292 diagnoses of tonsillar SCC during the study period. Therefore, approximately 1% of patients diagnosed with tonsillar SCC presented as an emergency with symptoms of PTA/PTC.

Shared clinical features

Multiple regression analysis was not feasible due to the very low number of OPSCC cases. In order to prevent possible identification of patients, we have also not reported linked demographic data such as exact age and gender. Despite this, there are still some shared clinical features that mark out all three patients from others presenting with symptoms of PTA/PTC.

Persistent pain – At the time of presentation, all three OPSCC patients reported a relatively long history of persistent unilateral sore throat, lasting between five and twenty weeks. They had all sought medical attention and treatment in the community. Two of the three patients also complained of persistent ipsilateral otalgia.

Aspirate-negative and unresponsive to antibiotics – There was no objective evidence of PTA in any of these patients. In two of the three patients where aspiration or incision and drainage were attempted, no pus was found. In the third patient, clinical suspicion of cancer

was so high that aspiration was not attempted. Administration of systemic antibiotics led only to transient improvements in pain and swallowing.

Risk factors – Two patients were over the age of 40. All three had significant exposure to smoking (more than 15 pack years) and/or alcohol (more than 20 units per week). Two patients had HPV-positive OPSCC based on in situ hybridisation of HPV16/18 DNA.

Cervical lymphadenopathy and tumour stage – Two patients had palpable ipsilateral neck masses at diagnosis but no distant metastases. All patients had locally advanced tumours (T3) and were treated with concurrent chemoradiation, with curative intent. Two of the three patients died from residual or recurrent OPSCC within twelve months of their diagnosis.

Audit of follow-up practices

During a one-year period (January 2016 – December 2016) 510 patients were identified to have a diagnosis of PTA/PTC through the coding system at each site (**Table 1**). Following a review of medical records, 298 patients were found to have PTA (59.4%), 151 had PTC (29.1%) and 61 had an incorrect diagnosis (such as tonsillitis, infectious mononucleosis or epiglottitis) yielding a clinical coding error rate of 11.9%.

Using the putative guideline discussed above and in **Table 2**, 106 patients (23%) would have been considered to be high risk based on age (≥40 years; n=88) or tonsillar asymmetry (n=18). Urgent follow up in the clinic was arranged for 73% of these patients, indicating high clinician risk awareness in the absence of hard data.

Admission volumes and socioeconomic factors

Admission volumes for PTA are detailed in **Table 3**. Mean admission rates per unit were greater at Aintree and the Royal Liverpool compared to other sites. Both Aintree and the Royal Liverpool are in the Liverpool local authority and their intakes are likely to reflect this urban population. However, Aintree University Hospital also receives admissions from Whiston, Southport and Ormskirk hospitals, and therefore the data from Knowsley are shown, as this was the most deprived ward served by that site [6].

DISCUSSION

Synopsis of key findings

The aim of this study was to address two questions: how many patients presenting with symptoms of PTA/PTC have an underlying diagnosis of OPSCC; do these patients present with an aspirate-positive quinsy or is it a case of symptoms mimicking a PTA?

In a cohort of 1975 inpatients recorded as having had PTA/PTC during a five-year period, we found the prevalence of OPSCC to be 0.15%, or approximately 1:650. No cancer patient had objective evidence of a PTA.

Around a quarter of patients presenting with PTA/PTC were found to have conventional high-risk features for malignancy, such as older age and tonsillar asymmetry. In the present cohort, 73% of patients were appropriately followed-up in clinic.

Study limitations and mitigation strategies

We acknowledge that the data gleaned are relatively crude given the retrospective nature of the project and its dependence on clinical coding. The shortcomings of clinical coding are well-documented, and we have tried to account for them in our method.

While a prospective study would provide better data, we feel that this would be a relatively inefficient use of scarce research resources. Our aim was to arrive at an estimation of prevalence to offer an insight into the risk of missed or delayed diagnosis, which is the underlying concern of many ENT clinicians.

This risk is low for most units. Our data suggest that most district general hospitals will admit between 30 to 60 PTA/PTC patients annually. Units with a predominantly urban population may see 90-100 admissions, up to more than 150 admissions per annum for larger hub or tertiary units. At 1:650 admissions, cancer masquerading as an abscess is therefore a relatively rare event.

Merseyside has a higher-than-average burden of head and neck cancers. The prevalence we report here might be an overestimation and not generalisable to other units around the UK or the world. Since the study relies on data linkage with a single regional database, some patients may have presented with a diagnosis of OPSCC outside the region and therefore, the lost-to-follow-up rate is unknown. However, from the authors' professional experience of cancer service provision within the region, we feel that this effect is small.

A larger, nationwide study would provide enough data to allow advanced statistical modelling. However, risk factors for OPSCC are well-described and the study aim was to gain an insight into the presentation of cancer patients in the acute, infective context. While larger volumes of data might be helpful, we suspect that further work would be subject to the law of diminishing returns.

Study strengths

To authors' knowledge this is the first study to determine the prevalence of OPSCC in a population of patients presenting with PTA/PTC. The study is based on a large cohort of patients followed over a significant time period from multiple centres. Social deprivation is closely related to the burden and mortality from head and neck cancers. Our study population represented a wide range of geographical and socioeconomic areas [7].

Socioeconomic perspective

Socioeconomic deprivation is known to impact upon prevalence of infectious disease and how this is treated. GPs in the UK prescribe more antibiotics for sore throats for those living in poor housing, in overcrowded conditions or living with poor nutrition or substance misuse [8].

In our study, there is a clear difference in the number of people presenting with PTA/PTC in each area (**Table 3**). Discrepancies in PTA admissions may be random, or they may reflect associations between socioeconomic deprivation and prevalence. Social deprivation has previously been shown to be the strongest predictor of Emergency Department (ED) attendance rates in England [9]. In our region, a third of the population lives in areas that

are among the most deprived quintile in England [7]. In keeping with this, more patients presented to the units serving the most deprived populations, including Knowsley (Health Index rank 144 of 149 local authorities), St Helen's (141) and Liverpool (137) and Halton (132) [6][10].

Almost a quarter of patients admitted with PTA/PTC in this study were identified as high risk, requiring follow up. Assuming one follow-up visit each, this would amount to 454 clinic visits per annum, with the attendant costs of the consultation and endoscopic examination. It seems likely that the cost of these follow-up visits would be borne chiefly by busier units in more socioeconomically deprived areas.

Comparison with other studies and clinical applicability

The literature on the association of peritonsillar infection and OPSCC is limited and largely case-report based [4,5]. In a study of 38 patients with OPSCC, Bannister and others reported that 18 of 38 had previously been treated for tonsillitis by their general practitioner (GP) with a mean of 1.9 visits prior to referral to secondary services [11]. The average time period from first presentation to GP and referral to ENT was 34 days (range 0-84 days). These findings suggest that patients with OPSCC commonly present in primary care with a sore throat and are often thought to have tonsillitis at first. Based on our data, the risk of OPSCC in patients treated in secondary care for PTA/PTC is very low.

In 2015, Rokkjaer and Klug reported a study on the histological rate of malignancy in patients diagnosed with peritonsillar abscess [12]. They identified one incidental case of acute myeloid leukaemia and no OPSCC in 275 adult patients undergoing tonsillectomy for PTA. This would fit well with the data presented in this study, from the point of view of both diagnosis as well as prevalence.

It is uncommon to perform 'hot' or 'quinsy' tonsillectomy in the UK. The data in our study support the idea that patients with OPSCC present with symptoms mimicking PTA/PTC, rather than an abscess. Establishment of the correct diagnosis is crucial, and this can be done on admission in a minimally invasive way, such as through a trial of needle aspiration.

Many units now offer either trans-oral laser or robotic surgery for selected OPSCC and ‘hot’ tonsillectomy for a mistaken diagnosis of PTA might limit the resective options open to the patient.

CONCLUSION

This study estimates the risk of OPSCC in patients presenting with peritonsillar symptoms. The prevalence is low, even in a region with a relatively heavy disease burden. Since PTA is a relatively common ENT emergency, being able to stratify the risk of cancer could help to rationalise services and inform both clinicians and patients.

Clinicians should, however, retain a high level of suspicion in patients with persistent symptoms, oropharyngeal asymmetry and significant alcohol and smoking history. Age alone may not be a sufficient discriminator.

299 **REFERENCES**

300 [1] Schache AG, Powell NG, Cuschieri KS, Robinson M, Leary S, Mehanna H, et al. HPV-
301 Related Oropharynx Cancer in the United Kingdom: An Evolution in the
302 Understanding of Disease Etiology. Cancer Res 2016;76:6598–606. doi:10.1158/0008-
303 5472.CAN-16-0633.
304 [2] Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, et al. Human
305 papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med
306 2010;363:24–35. doi:10.1056/NEJMoa0912217.
307 [3] McIlwain WR, Sood AJ, Nguyen SA, Day TA. Initial symptoms in patients with HPV-
308 positive and HPV-negative oropharyngeal cancer. JAMA Otolaryngol - Head Neck Surg
309 2014;140:441–7. doi:10.1001/jamaoto.2014.141.
310 [4] Holmes SB, Vora K, Hardee PSG. Squamous cell carcinoma presenting as peritonsillar
311 abscess. Br J Oral Maxillofac Surg 2001;39:46–8. doi:10.1054/bjom.2000.0567.
312 [5] Fort MM, Gathings R, Domanski MC. Squamous cell carcinoma of the tonsil
313 masquerading as a peritonsillar abscess. Am J Emerg Med 2013;31:1002.e3-1002.e4.
314 doi:10.1016/j.ajem.2013.02.015.
315 [6] The UK Office of Nationall Stastistics (ONS) Health Index Explorer n.d.
316 https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/
317 populationestimates/datasets/
318 populationestimatesforukenglandandwalesscotlandandnorthernireland (accessed
319 February 26, 2021).
320 [7] Taib BG, Oakley J, Dailey Y, Hodge I, Wright P, du Plessis R, et al. Socioeconomic
321 deprivation and the burden of head and neck cancer—Regional variations of
322 incidence and mortality in Merseyside and Cheshire, North West, England. Clin
323 Otolaryngol 2018. doi:10.1111/coa.13067.
324 [8] Kumar S, Little P, Britten N. Why do general practitioners prescribe antibiotics for sore
325 throat? Grounded theory interview study. Br Med J 2003;326:138.
326 doi:10.1136/bmj.326.7381.138.
327 [9] Scantlebury R, Durbaba S, Sidhu K, Ashworth M, Rowlands G, Schofield P.
328 Socioeconomic deprivation and accident and emergency attendances: Cross-sectional
329 analysis of general practices in England. Br J Gen Pract 2015;65:e649-54. doi:10.3399/

bjgp15X686893.

[10] Pearson-Stuttard J, Davies SC. The Health Index for England. Lancet 2021;397:665. doi:10.1016/S0140-6736(21)00201-4.

[11] Bannister M, Ah-See KW. Is oropharyngeal cancer being misdiagnosed as acute tonsillitis? Br J Gen Pract 2014;64:e742–4. doi:10.3399/bjgp14X682537.

[12] Rokkjaer MS, Klug TE. Tonsillar malignancy in adult patients with peritonsillar abscess: retrospective study of 275 patients and review of the literature. Eur Arch Oto-Rhino-Laryngology Off J Eur Fed Oto-Rhino-Laryngological Soc Affil with Ger Soc Oto-Rhino-Laryngology - Head Neck Surg 2015;272:2439–44. doi:10.1007/s00405-014-3186-0.