Facial Pain as First Manifestation of Lung Cancer: A Case of Lung Cancer–Related Cluster Headache and a Review of the Literature

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Facial pain can, on rare occasions, be the presenting symptom of lung cancer. This report describes a patient with non-metastatic lung cancer, which was associated with attacks of debilitating facial pain, presenting as cluster headache. Moreover, 32 reported cases of lung cancer–related facial pain (including the present one) are reviewed, and their clinical features are summarized. The facial pain is almost always unilateral, and is most commonly localized to the ear, the jaws, and the temporal region. The pain is frequently described as severe and aching, and may be continuous or intermittent. Aggravation and expansion of the pain, digital clubbing, increased erythrocyte sedimentation rate, and hypertrophic osteopathy, may contribute to the diagnosis. Referred pain, due to invasion or compression of the vagus nerve, as well as paraneoplastic syndrome secondary to the production of circulating humoral factors by the malignant tumor cells, is implicated in the pathophysiology of facial pain associated with non-metastatic lung cancer. Radiotherapy and tumor resection with vagotomy are very effective in aborting the facial pain. Thus, lung cancer should be included in the differential diagnosis of facial pain that is atypical and/or refractory to treatment. J OROFAC PAIN 2003;17:262–267.

Key words: cluster headache, facial pain, lung cancer, referred pain, vagus nerve

Facial pain can, on rare occasions, be the presenting symptom of non-metastatic lung cancer. The presentation of facial pain as a first symptom of non-metastatic lung cancer was first reported by Des Prez and Freemon in 1983.[1] To date, 31 cases of facial pain associated with non-metastatic lung cancer have been reported in the English language literature.[1–11] Only 1 of these 31 cases was presented in the dental literature.[11] It is important that dentists and orofacial pain specialists are familiar with the association between lung cancer and facial pain, since such pain is commonly misdiagnosed as atypical facial pain, dental pain, or pain associated with temporomandibular disorders (TMD) or trigeminal neuralgia.

The authors describe a case of cluster headache associated with lung cancer, and review the 32 cases, in order to further elucidate the clinical features of this type of pain (Tables 1 and 2).[1–11]

Table 1 Clinical Features in 32 Patients with Lung Cancer–Related Facial Pain

	Reference	Age, sex	Right/ left	Mo	Site of pain	Type of pain	Pain duration	Smoker	DC	ESR
1	1	45 M	R	4	Maxilla; later face, neck	Deep, boring	Constant	NR	NR	Elevated
2	2	60 M	R	4	Lower jaw, ear; later oropharynx	Aching, shooting	NR	Yes	NR	NR
3	2	53 F	L	2.5	Ear, temporal	NR	NR	Ex	NR	47
4	3	66 F	L	NR	Face	NR	NR	NR	NR	NR
5	4	62 F	R	36	Ear, jaw	Aching	NR	Yes	NR	NR
6	4	59 F	R	48	Temporomandibular; later ear, face	Aching	NR	Yes	NR	Elevated
7	4	39 F	R	4	Ear, throat; later face	NR	NR	Yes	NR	NR
8	4	54 M	L	1	Periorbital; later face	Sharp	Several hours	Yes	NR	NR
9	4	48 M	R	4	Ear; later jaw, face	Aching	NR	NR	NR	NR
10	4	34 M	R, rarely L	9	Teeth, ear	"Nagging ache"	Constant	Yes	NR	NR
11	4	69 F	R	16	Lower jaw, forehead, ear	Aching, episodes of sharp pain	NR	Yes	NR	NR
12	4	78 M	R	12–18	Ear, eye, face	Severe ache	NR	Ex	NR	NR
13	5	41 M	L	12	Ear, retro-orbital	Aching	NR	Yes	NR	NR
14	6	53 F	R	12	Teeth; later ear, nostrum	Severe, aching	Constant	Yes	Yes	NR
15	6	38 F	R	8	Teeth, ear	Dull, aching	NR	Yes	Yes	NR
16	6	40 M	L	2	Cheek, ear	Severe	"Longlasting bouts"	Yes	Yes	NR
17	7	60 F	L; later R and L	8	Temporal, ear	Sharp; later paroxysmal	4–5 times/day for 5 minutes	Yes	NR	NR
18	7	47 F	R	3	Jaw, ear, temporal	Burning with paroxysmal worsening	Constant	Ex	Yes	NR
19	8	50 F	L	6	Ear	NR	NR	Yes	NR	NR
20	9	68 F	R	12	Ear, temporal, jaw	Severe, aching; episodes of sharp pain	Constant; sharp pain lasted min	Ex	Yes	36
21	9	57 F	L	5	Ear, jaw	Excruciating, aching, boring	Intermittent; later constant	Ex	NR	7
22	9	49 F	L	1	Ear, eye, temporal, neck	Severe, aching	Constant	Ex	NR	105
23	9	50 M	R	4	Jaw, ear, temporal, neck, shoulder	Severe, aching	Constant	Yes	Yes	80
24	9	44 F	L	7	Cheek, ear, nostril	Severe, aching	Constant	Ex	NR	10
25	9	65 M	R	17	Jaw, throat, eye	Severe, aching	Constant	Ex	NR	85
26	9	64 F	R	24	Ear, temporal, jaw	Severe, aching	Intermittent, hours	Yes	Yes	8
27	9	72 M	L	1	Ear, temporal, jaw	Severe, aching	Intermittent, 30–120 minutes	Yes	NR	NR
28	9	62 F	L	3	Cheek, nostril, eye	Severe, aching	Constant	Ex	No	69
29	9	72 F	L	1	Ear, cheek, jaw, temporal	Severe, aching	Constant	Yes	NR	83
30	10	45 F	R	9	Preauricular; later temporal, maxillary	Severe, dull, throbbing	Episodic; later constant	NR	NR	NR
31	11	NR F	R	10	Lower jaw	Aching	Constant	Yes	NR	NR
32	PR	37 M	R	1.5	Periorbital region	Severe	Intermittent, hours	No	No	Normal

DC = digital clubbing, ESR = erythrocyte sedimentation rate (normal 0–29 mm/h), F = female, M = male, Mo = months in pain prior to diagnosis, NR = not reported/recorded, PR = present report.

Table 2 Findings in 32 Patients with Lung Cancer–Related Facial Pain

	Associated subsequent symptoms	Prior diagnoses	Prior dental treatment	Cancer type	Brain and/or head CT/MRI	Treatment	Pain relief
1	Fullness in right ear, weight loss	AFP	NR	AC	Head CT normal	Tumor resection, vagotomy	Complete
2	Haemoptysis, chest wall ache	Dental pain	Root fillings, extractions	PD, AC	NR	Vagotomy	NR
3	NR	NR	NR	PD	Brain CT old infarct	NR	NR
4	Haemoptysis, weight loss	NR	Extractions	SCC	NR	Pneumonectomy, vagotomy	NR
5	NR	NR	NR	SC	Brain CT normal	Radiotherapy	Complete
6	Weight loss, haemoptysis	NR	NR	PD, SCC	Brain CT normal	Radiotherapy	Complete
7	Haemoptysis	NR	NR	UD	NR	Radiotherapy	Complete
8	Hoarseness, vocal cord paresis	NR	NR	NR	Brain CT normal	Radiotherapy	Complete
9	Chest wall pain	NR	NR	PD, SCC	NR	Radiotherapy	Complete
10	NR	AFP	NR	PD, AC	Head CT normal	Chemotherapy, radiotherapy	Complete after RT
11	NR	NR	NR	PD, AC	NR	Radiotherapy	Complete
12	NR	NR	NR	PD, AC	NR	Tumor resection	Good
13	Vocal cord paresis, thoracic pain	NR	NR	PD, SCC	Head MRI normal	Chemotherapy, radiotherapy	Complete after RT
14	Persistent cough	Dental pain	Extractions	UD, AC	Brain CT normal	Radiotherapy	Complete
15	Hypertrophic osteoarthropathy	Dental pain	Extractions	PD	Brain CT normal	Radiotherapy	Complete
16	Hypertrophic osteoarthropathy	NR	NR	AC	Brain CT normal	Lobectomy, nodectomy	Complete
17	Nausea, vomiting	TMD	NR	SC	Brain CT normal	Chemotherapy	Good
18	Arthralgias	NR	NR	AC	Brain CT normal	None	—
19	NR	NR	NR	SCC	NR	Tumor resection	Complete
20	Weight loss	TN, AFP	Extractions	AC	Head MRI normal	Radiotherapy	"Better"
21	Weight loss	NR	NR	CARC	Head CT/MRI normal	Radiotherapy, chemotherapy	Good
22	Weight loss	NR	NR	AC	Head CT/MRI normal	Radiotherapy	Good
23	Weight loss	NR	NR	SCC/AC	Head CT normal	Radiotherapy	Good
24	NR	NR	NR	Atypical CARC	Head CT normal	Radiotherapy	Good
25	Weight loss	NR	NR	SC/UD	Head CT/MRI normal	Pneumonectomy, radiotherapy	Good
26	NR	NR	NR	SCC	Head CT normal	NR	NR
27	Weight loss	NR	NR	AC	Head CT normal	NR	NR
28	Weight loss	NR	NR	LC, UD	Head CT normal	NR	NR
29	NR	NR	NR	AC	Head CT normal	NR	NR
30	Lethargy, weight loss, haemoptysis	Atypical TN	NR	AC	Brain CT/MRI, head CT normal	Radiotherapy	Complete
31	Weight loss, persistent cough	TMD, neuralgia	None	LC, NE	Sinus CT, jaw MRI normal	Pneumonectomy	Complete
32	Nasal drainage, nausea	Sinusitus TMD, CH	None	Non-SC	Brain CT/MRI normal	Tumor resection, vagotomy	Complete

AC = adenocarcinoma, AFP = atypical facial pain, CARC = carcinoid, CH = cluster headache, LC = large cell carcinoma, NE = neuroendocrine cancer, NR = not reported/recorded, PD = poorly differentiated cancer, RT = radiation therapy, SC = small cell cancer, SCC = squamous cell cancer, TMD = temporomandibular disorders, TMJ = temporomandibular joint, TN = trigeminal neuralgia, UD = undifferentiated cancer.

Case Report

A 37-year-old, non-smoker, Caucasian male presented with pain of 1-month duration, in the right periorbital region. According to the patient, the facial pain started 1 week following trauma to the left side of the face. The pain had been previously diagnosed as sinusitis and temporomandibular joint dysfunction, and had been unsuccessfully treated with decongestants, antibiotics, muscle relaxants, and non-steroidal anti-inflammatory drugs. The wearing of a mouthguard had provided no relief. The pain occurred several times per day and lasted for 2 to 3 hours; it was described as severe (pain intensity "9" on a 0 to 10 numerical rating scale, where 0 represented "no pain" and 10 "worst imaginable pain"), interrupted sleep, and was exacerbated by coughing. The episodes were associated with rhinorrhea and nausea. The patient was provisionally diagnosed with cluster headache and prescribed oxygen. Oxygen reduced the pain intensity to "5 to 6," but elicited coughing, which was intolerable. The pain was refractory to lidocaine nasal drops, verapamil and prednisone, while divalproex sodium reduced pain intensity to "7." Sinus and brain computerized tomography (CT) scans and a brain magnetic resonance imaging (MRI) examination were normal. A CT scan of the thorax revealed a mass in the right upper lobe, with associated right paratracheal adenopathy. Biopsy of the lung lesion was performed and pathologic examination revealed non-small cell lung cancer. Following surgical removal of the tumor with vagotomy, the facial pain resolved completely. No sensory or motor deficits were noted following vagotomy. The patient remained pain-free for 4 months, until relapse of the lung cancer resulted in recurrence of the right-sided facial pain. Chemotherapy was ineffective and the patient died a few months later.

Discussion

On rare occasions, facial pain can be the first manifestation of non-metastatic lung cancer. Our review revealed 32 patients (including our case) comprising 12 males (37.5%) and 20 females (62.5%), reflecting a female-to-male ratio of 1.67:1. The cases are specified in Tables 1 and 2. The mean age at presentation was 54 years (range 34 to 78). The vast majority of the patients were smokers or former smokers. The facial pain preceded the diagnosis of lung cancer by a mean of 9 months (range 1 to 48).

Pain Site

Facial pain related to non-metastatic lung cancer was almost invariably unilateral, always ipsilateral to the tumor. Out of the 32 cases reviewed, 18 (56.25%) involved right-sided pain, and 12 (37.5%) left-sided pain. Bilateral pain was present only in 2 cases (6.25%); in 1 of these the contralateral side was affected to a much lesser degree, while in the other the pain spread to the contralateral side of the face later in the course of the disease.[4,7] The pain most commonly affected the ear, the jaws, and the temporal region. Pain in or around the ear was present in 20 of the 32 cases (62.5%), and jaw pain in 14 cases (43.75%). The pain may also be localized in or around the eye, as in the present case, as well as in the teeth, throat, and neck. Lung cancer–related pain affecting the forehead or the shoulder has also been reported. Occasionally, the pain gradually spread to involve the whole face.

Pain Quality and Duration

Most patients presented with continuous pain (in 13 of the 19 cases where pain duration was reported). However, the pain may also be intermittent, usually lasting for hours, as was the case for our patient. Episodic pain may gradually become constant as the disease progresses.[9,10] The pain is typically described as severe and aching. Occasionally, episodes of sharp, paroxysmal pain occur.[4,9] Burning, shooting, or throbbing pain has also been described.[2,7,10]

Associated Symptoms

An elevated erythrocyte sedimentation rate (ESR), digital clubbing, and hypertrophic osteopathy have been observed in some patients, and may suggest the presence of an underlying lung carcinoma in patients with atypical facial pain.[6,9] The most common symptoms that evolved in the course of the disease were weight loss, haemoptysis, persistent cough, and chest wall ache. Some patients also developed vocal cord paralysis and hoarseness. Infrequently, nausea, vomiting, arthralgias, and lethargy may accompany the facial pain. In the present case the facial pain was associated with nasal drainage, and presented as cluster headache.

Histopathology

The most common histologic type of lung carcinoma presenting with facial pain was adenocarcinoma

(41%), followed by squamous cell (19%), and small cell carcinoma (9%). Facial pain related to non-metastatic lung cancer has also been reported with other histologic types of carcinoma, such as poorly differentiated, undifferentiated, large cell neuroendocrine, and non-small cell carcinoma.[2,4,6,11]

Differential Diagnosis

Usually, the medical and dental assessment of a patient with facial pain associated with non-metastatic lung cancer rules out head and neck pathology, leading to the diagnosis of atypical facial pain.[1,4,9] On the other hand, the pain may be localized in the teeth and mimic dental pain. There are reports of patients who underwent unnecessary irreversible dental treatments such as root fillings and extractions.[2,6,9] Diagnostic anesthetic blocks are important in helping differentiate pain of dental origin from heterotopic pains, and should be used routinely in the dental practice when tooth pain is encountered in the absence of obvious dental pathology.[12]

Lung cancer–related facial pain may also be confused with pain associated with TMD, especially when the jaws and the ear are involved.[7,11] Nonetheless, TMD are characterized usually by pain of mild or moderate intensity that is aggravated by the function of the mandible.

Cases where episodes of sharp pain occur may be misdiagnosed as trigeminal neuralgia.[9,10] However, the pain attacks in trigeminal neuralgia are typically much shorter and can be triggered by innocuous stimulation. In addition, carbamazepine is very effective in alleviating the pain in trigeminal neuralgia, while it has no benefit in lung cancer–related pain.

In the present case, the facial pain presented as cluster headache. Cluster headache is characterized by attacks of severe unilateral pain that is localized in the orbital, supraorbital, and/or temporal region, lasts 15 to 180 minutes, and is associated with autonomic symptoms, such as lacrimation and rhinorrhea.[13] The fact that the pain fulfilled the diagnostic criteria for cluster headache and responded partially to oxygen, a first line abortive treatment of cluster headache, suggests that our patient actually experienced cluster headache. However, elimination of the pain immediately following surgical removal of the tumor and vagotomy, and recurrence of the pain only upon relapse of the lung cancer, indicate that the cluster headache was a consequence of lung cancer. Tajti et al (1996) reported on a patient with cluster-like headache secondary to brain metastases of lung cancer.[14] To our knowledge, the present case is the first report of cluster headache related to non-metastatic lung cancer.

Pathophysiology

A mechanism that may underlie facial pain associated with non-metastatic lung cancer is referred pain, following local invasion or compression of the vagus nerve.[4] Most vagal afferents terminate in the nucleus solitarius; however, a few fibers branch and terminate in the spinal trigeminal nucleus, thus providing a potential neuroanatomic substrate for vagus nerve–mediated referred facial pain.[15–18]

Circulating humoral factors produced by malignant tumor cells may also be responsible for the genesis of facial pain in the presence of lung cancer. These humoral factors, as well as autoimmune phenomena, are thought to account for the development of various lung cancer–related paraneoplastic syndromes, including Cushing's syndrome, reflex sympathetic dystrophy, and visual loss.[19–21] Notably, cytokines, such as tumor necrosis factor (TNF) and interleukin-1 (IL-1), are increased in patients with malignant tumors.[22,23] These cytokines have been implicated in the pathophysiology of cluster headache.[24,25] Accordingly, it has been suggested that TNF and IL-1 may play an important role in the onset of cancer-related cluster headache.[14] Relatedly, the levels of calcitonin gene-related peptide (CGRP) and vasoactive intestinal peptide (VIP), known mediators of paraneoplastic processes in patients with lung cancer,[19] are also increased in cluster headache patients,[26] further suggesting that lung cancer–related cluster headache may constitute a paraneoplastic syndrome. Moreover, release of VIP has been associated with the nasal congestion and rhinorrhea that often accompany cluster headache attacks.[26]

The cluster headache in the present case was completely aborted following surgical removal of the tumor and the entrapped branches of the vagus nerve, while it recurred upon relapse of the lung cancer. The latter might have resulted in production of humoral factors by the tumor cells; invasion of neighboring intact branches of the vagus nerve by the recurrent tumor is also possible. Accordingly, the cluster headache in our patient could represent a paraneoplastic syndrome, secondary to secretion of biologically active agents, such as cytokines, CGRP, and VIP from the lung cancer cells. Production of VIP by the tumor might also account for the associated rhinorrhea in the present case. Additionally, referred pain mediated through the residual branches of the vagus nerve

could also conceivably contribute to cluster headache.

Treatment

Radiotherapy of the lung cancer offered good or complete facial pain relief in all patients. Tumor resection and vagotomy were also very effective. On the other hand, chemotherapy alleviated the facial pain only in 1 out of the 3 patients who underwent this treatment.[4,5,7] Notably, subsequent radiation therapy completely aborted the facial pain in the 2 patients who did not benefit from chemotherapy.[4,5]

Conclusions

Facial pain in the absence of obvious head and neck pathology should prompt extensive investigation to reveal the underlying etiology. Lung cancer should be considered in the differential diagnosis, and a chest x-ray and/or CT should be included in the assessment, especially when the patient is a former or a current smoker. Localization of the pain in or around the ear, aggravation and expansion of the pain, digital clubbing, increased ESR, and hypertrophic osteopathy may contribute to the diagnosis. Weight loss, haemoptysis, persistent cough, and thoracic ache are the most common symptoms that succeed the facial pain, leading to the diagnosis. Histopathologic examination of the lung lesion is necessary to render the final diagnosis. Also, MRI and CT of the brain and the head are indicated to rule out a cephalic metastasis as the cause of the facial pain.

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