Correspondence and Clinical Notes

Clinical Notes

Lung Cancer Presenting With Unilateral Facial Pain: Remission After Laryngeal Nerve Palsy

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A 39-year-old woman presented with a 2-month history of intractable, left-sided facial pain. A CT scan of the thorax disclosed a large lung mass surrounding supra-aortic vessels and hilus. The symptoms underwent a rapid and spontaneous remission after laryngeal nerve palsy with dysphonia developed. Referred facial pain secondary to the compression of the vagus nerve can rarely be the first manifestation of an underlying lung cancer. All cases of unexplained unilateral facial pain should be investigated for a mediastinal pathology, especially in smoker subjects.

Key words: facial pain, lung cancer

Facial pain is a common clinical symptom with a wide spectrum of underlying conditions, including neurological, odontological, and otolaryngological pathologies. Atypical or idiopathic facial pain is defined as a persistent pain syndrome of unknown origin not attributed to another disorder. Rarely, facial pain can be the consequence of diseases involving the thorax, particularly a lung mass. In these cases, the symptoms may be initially misinterpreted for atypical facial pain. We describe a patient in whom facial pain was the presentation symptom of a remote lung carcinoma.

CASE REPORT

A 39-year-old woman presented with a 2-month history of left-sided facial pain. She experienced a gradual onset, constant, dull pain localized in the superior alveolar and zygomatic regions. The pain was continuous, moderate to severe in intensity, with superimposed exacerbations of excruciating severe, stabbing pain, usually radiating toward the frontal and orbital areas, and associated with tearing, eye redness, and mild nausea. Her past medical history was not significant, with the exception of occasional bouts of unilateral, throbbing headaches, usually during the period of menses, typical of migraine without aura. She had been smoking 1 pack of cigarettes a day, for at least 20 years.

Because of her symptoms, the patient was referred to an odontologist who excluded a dental pathology. A magnetic resonance imaging of the brain and a carotid Doppler ultrasound were normal. The patient was administered gabapentin, carabamazepine, and prednisone without improvement. About 2 weeks prior to the visit, cough and poor appetite developed.

At presentation, the patient was still symptomatic, even if the pain had mildly diminished. The neurological examination was unremarkable, with the exception of a tenderness over the left maxillary region. The physical examination disclosed a supraclavear lymphadenopathy on the right. Auscultation of the lungs revealed diminished breath sounds in the left-upper lobe. Cardiac examination was normal. A CT scan of the chest was scheduled on the basis of a suspected lung mass. A few days after her evaluation, the patient...
became dysphonic. A subsequent examination by an oto-
laryngologist revealed a paresis in adduction of the left vo-
cal cord. The CT scan of the chest showed a large solid
mass in the superior aspect of the left mediastinum sur-
rounding supra-aortic vessels and hilus, markedly effacing
the mainstem bronchus, and displacing trachea and vena
cava (Fig.). A fine-needle biopsy of supraclavear node con-
firmed the presence of a large cell carcinoma. A complete
blood count was normal, except for a mild anemia. The ESR
was markedly elevated at 83 mm/h. In the following days,
the facial pain gradually improved and then spontaneously
ceased. A left cervicobrachial pain with hand paresthesia
rapidly built-up.

The patient was treated with chemotherapy (gem-
citabine and cisplatin), with partial improvement of dyspho-
nia and cervicobrachial pain. Facial pain did not recur at a
6-month follow-up.

COMMENTS

Referred facial pain is a rare symptom of nonmetastatic
lung malignant lesions. Des Prez and Freemon described in
1983 the first patient suffering from facial pain thought to
be secondary to a lung mass, and other cases have been
described in the recent years. The presumed mechanism
by which a thoracic mass can provoke a pain referred to
the face is compression or infiltration of the vagus nerve.
The vagus is a mixed nerve providing motor, sensory, and
parasympathetic innervation of the pharynx, larynx, thorax,
and abdomen. Pain signals originating from the thoracic and
abdominal viscera are driven by general visceral afferents,
and via the ganglion nodosum reach the nucleus solitarius in
the medulla. Convergence of the general visceral afferents
and general somatic afferents at the level of the descending
nucleus of the trigeminal system may explain the ipsilateral
referred facial pain.

In most of the described patients, pain is perceived in
the ear over the territory supplied by the auricular ramus
that carry the general somatic afferents of vagus nerve. In
our patient, continuous and often incapacitating pain was
localized in the maxilla with radiation at the whole terri-
tory of the ophthalmic division of trigeminal nerve. Facial
pain preceded first symptoms of carcinoma, such as cough
and weight loss, by almost 2 months, and was intractable by
common drugs. Unlike past reported cases, our patient un-
derwent a spontaneous relief of the pain when a cordal palsy
developed, presumably following the extension of tumor and
compression of recurrent laryngeal nerve as well. Therefore,
we can argue that at least partial integrity of the vagus nerve
is necessary in determining the referred pain.

Facial pain is a complex clinical syndrome, sometimes
secondary to a number of extracranial pathologies for which
an early diagnosis is needed. In every smoker patient with
unilateral facial pain, especially if persistent and/or severe,
a chest radiograph is mandatory. In cases with a high in-
dex of suspicion of lung neoplasm, particularly if the pa-
tient has weight loss, cough, hemoptysis, or elevated ESR,
a CT scan must be performed even if X-ray should be
normal.
REFERENCES

Reversible Palinopsia and the Alice in Wonderland Syndrome Associated With Topiramate Use in Migraineurs

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Two patients are reported who developed palinopsia while taking topiramate for migraine prevention which resolved or decreased in frequency or duration on lower doses, but recurred or increased in frequency or duration on higher doses. Both patients had complete resolution of palinopsia when topiramate was discontinued. A third patient is described who developed the “Alice in Wonderland” syndrome about 1 week after starting topiramate for migraine prevention with complete resolution of symptoms about 1 month after stopping. Topiramate use may cause palinopsia and may be associated with the Alice in Wonderland syndrome through an unknown mechanism.

Key words: palinopsia, Alice in Wonderland syndrome, topiramate

Palinopsia (from Greek: palin, again and opsis, vision) is the symptom of persistent or recurrent visual images following removal of the exciting stimulus. “In some cases patients see a series of ‘echoes’ of the object, separate from but in proximity and identical to the actual object, giving the impression of polyopia (cerebral polyopia).” Two patients are reported who developed palinopsia while taking topiramate for migraine prevention.

In the “Alice in Wonderland” syndrome, patients experience distortion in body image characterized by enlargement, diminution, or distortion of part of or the whole body, which they know is not real. A patient is discussed who developed the syndrome shortly after starting on topiramate.
CASE 1
This 57-year-old woman has had recurring headaches since the age of 10. She described more a right-sided than left-sided throbbing, which could be severe and associated with nausea, light and noise sensitivity, and vomiting in the past. She had had a visual aura, seeing zigzags lasting for 20 to 30 minutes before the headaches, which has not occurred for about 1 year. Three years previously, the headaches increased to a daily basis without medication overuse. An MRI of the brain was normal. She was placed on a slowly increasing dose of topiramate to 200 mg at bedtime over 8 months, and the headaches decreased to 1–2 monthly responsive to oral sumatriptan.

She was seen again 2½ years later, with a 5-month history of visual complaints. The symptoms, in the morning, initially occurred for only a few seconds and then gradually increased to constantly present for 1 hour and then gradually resolving over about 2 hours. She would see the outline of stationary people or if she moved her hand, she would see multiple hands or see multiple people if she looked at someone moving. Two months previously, when her headaches increased from 3 per month to 5 per month, her primary care physician increased the dose of topiramate by adding 25 mg in the morning. Over the next 2 months, the headaches decreased in frequency.

She also reported that for 1½ years, her balance seemed off. She had intermittent neck pain without radicular symptoms. She had no paresthesias or cognitive symptoms. There was a past medical history of restless legs symptoms, better with gabapentin 100 mg tid and clonazepam 0.5 mg at bedtime, and hypertension controlled with lisinopril and hydrochlorothiazide. She was also on trazadone 100 mg at bedtime for insomnia, which she had been taking for 1 month. Neurological examination was normal except for mildly diminished cold sensation and vibratory sense distally in both lower extremities and mildly unsteady tandem gait.

MRI of the brain and cervical spine were normal. Thyroid function studies were normal. A vitamin B12 level was low normal at 285 pg/mL (reference range 200 to 1100 pg/mL). Serum methylmalonic acid level was elevated at 435 nmol/L (reference range 88 to 243 nmol/L). A complete examination by a neuro-ophthalmologist was normal. She was started on vitamin B12 injections.

On a follow-up visit 10 weeks later, she reported that 3 months previously, she had run out of topiramate for 2 weeks and that her visual symptoms were a lot less frequent. She then restarted the topiramate at the full dose and the visual symptoms increased in duration as before. Three weeks previously, she ran out of 200 mg topiramate tablets and was taking only 25 mg at bedtime. The visual symptoms were again less lasting, for about 1 hour per day. I advised her to completely discontinue the topiramate. She kept a diary of her symptoms, which gradually decreased in duration until they completely resolved after 23 days. On a follow-up visit 5 weeks later, her balance was normal. Her migraines had increased in frequency from 3 per month on topiramate to 5 in the following month.

CASE 2
This 43-year-old woman has a 25-year history of headaches which were occurring about 15 days per month for the prior few years and previously a few times per month. She described a bifrontal or back of the head or behind the left or right eye throbbing of moderate to severe intensity associated with nausea, light and noise sensitivity, occasionally vomiting but no aura. She was taking 500 mg acetaminophen 4 to 6 times daily. There was a history of 5 ear operations for a cholesteatoma. Neurological examination was normal.

She was diagnosed with chronic migraine with suspected medication rebound and advised to discontinue the acetaminophen. She was started on preventive therapy with topiramate 25 mg daily for 1 week, to be increased by 25 mg weekly to 100 mg daily, baclofen 10 mg ½ to 1 tid prn headache, and sumatriptan 100 mg prn headache not to be used more than 2 days per week.

On a follow-up visit 1 month later, she reported that when she began topiramate 75 mg daily, she saw shadow images of objects a few times if it was dark. On her own, she decreased the topiramate to 25 mg daily, and the visual symptoms resolved. The headaches had decreased to 6 in the following month. I advised her to increase the topiramate again by 25 mg per week to 100 mg per day. An MRI scan of the brain was normal except for postoperative changes in the right mastoid. A complete examination by a neuro-ophthalmologist was normal.

On follow-up 7 weeks later, she reported that she started to see shadow images of moving objects or lights, which would be constant at night or in the dark and cause trouble while driving when she was on topiramate 75 mg daily again. She then adjusted the dose of the medication on her own. When she decreased the dose to 50 mg, the symptoms resolved in a few days. When she titrated up to 75 mg again, she had no visual symptoms; but at 100 mg a day, the symptoms recurred. When she decreased the dose to 50 mg a day, the symptoms resolved after about 4 days. The topiramate was discontinued.

COMMENTS
Palinopsia usually localizes to the nondominant occipitotemporal cortex with an uncertain underlying mechanism.
Palinopsia has numerous causes and associations including migraines, seizures (temporal, occipital, and periodic lateralized epileptiform discharges), focal cerebral lesions (trauma, parasite, abscess, stroke, tumor, arteriovenous malformation), Creutzfeldt-Jakob disease, metabolic (carbon monoxide poisoning and nonketotic hyperglycemia), multisple sclerosis, psychiatric disease (psychosis and schizophrenia), Charles Bonnet syndrome, in otherwise healthy individuals, and in patients with disease apparently confined to the eye or the optic nerve.

Palinopsia has also been reported with the use of drugs including antidepressants (trazadone, maprotiline, nafazodone), risperidone, clo miphen, interleukin 2, and illicits (lysergic acid diethylamide [LSD], headache (case 1). However, these details were not included. The first episode started about 1 week after starting on topiramate 25 mg at bedtime, which was increased by 25 mg weekly to 100 mg at bedtime. The episodes would occur in the morning. After numerous episodes, the topiramate was discontinued 2 months after initiation on a follow-up visit. She insisted that her symptoms were due to topiramate and I disagreed. She did not come back to see me. When I called the patient 2 years and 9 months later, she told me that the episodes of the “Alice in Wonderland” syndrome gradually decreased until resolving completely after about 1 month without any further recurrence.

The “Alice in Wonderland” syndrome is believed to derive predominantly from the nondominant posterior parietal lobe. It is most commonly due to migraines, but has also been reported after viral encephalitis (especially after Epstein-Barr virus) and as an epileptic phenomenon. Although the occurrence in this case could be due to migraine, and the occurrence and resolution could be by chance, the timing suggests an association with topiramate. However, there was no rechallenge with medication as in the first 2 cases. As in case 1, she also took the topiramate at bedtime and the visual symptoms were present in the morning. I am not certain if this suggests a relationship to brain receptor concentrations or activity.

Topiramate has a variety of mechanisms, including modulation of voltage-gated sodium ion channels, potentiation of (gamma)-aminobutyric acid inhibition, blocking of excitatory glutamate transmission, modulation of voltage-gated calcium ion channels, and inhibition of carbonic anhydrase. Animal studies suggest that topiramate may prevent migraine by inhibition of trigeminovascular neurons and cortical spreading depression.

I do not know how topiramate might cause reversible palinopsia or perhaps the “Alice in Wonderland” syndrome in migraineurs. As both conditions occur in migraine, it would be easy to conclude that their occurrence might be due to migraine rather than topiramate. As over 4 million patients have been exposed to topiramate worldwide for a variety of indications (including epilepsy where there could again be etiologic confusion if cases did occur, since seizures can also be a cause of both visual symptoms), it will be of interest to see if additional cases come to attention, and whether migraineurs are particularly susceptible.

Conflicts of Interest: None

REFERENCES


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**Efficacy of Therapeutic Intervention in Headache Units in Patients With Frequent Headaches: The EFUNCE Study**

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Data confirming that therapeutic intervention in headache units is superior to care received by patients in other levels of the health system are scant. This is a pilot study that includes patients seen in 4 headache units for at least 1 year, who had a headache frequency of more than 15 days per month. The results of the first 30 patients showed a significant improvement in different headache parameters and a high degree of satisfaction with the treatment received.

Key words: headache units, tertiary headache centers, efficiency

Headache disorders are a global public-health problem because they are frequent and disabling lifelong diseases. Effective health care can relieve much of the symptom burden of most headache disorders, and thereby mitigate both the human and financial costs. Most patients with headaches who seek care are treated in a primary care setting. This care could be appropriate and effective in many patients, but often other comorbid illnesses, behavioral problems, or excesses in treatment exist, requiring a specialized approach. A longitudinal study of patients with headaches treated in a primary care setting showed that 20% of them continue with significant pain and disability at 2 years.

These factors underscore the need for tertiary headache care. While the need for such systems of care may be clear, it remains necessary for such systems of care to demonstrate their impact on headache and other cost-sensitive figures of outcome. The value of this approach is well documented in the field of pain. There are few data underscoring the effectiveness of specialized tertiary headache clinics and only recently there are some data coming from an academic headache clinic.

For these reasons, we decide to investigate the efficacy of headache clinics in the treatment of headache in Spain. In this report, we present the pilot study that was done in 4 different headache units with the aim of evaluating the efficacy of therapeutic intervention in headache units in comparison with other care levels in order to validate a protocol.
that would allow us to carry out a big prospective program. (EFUNCE study: Eficacia de las Unidades de Cefalea. Efficacy of Headache Units)

MATERIALS AND METHODS
For this pilot study, we retrospectively analyzed the clinical records of a group of patients attending headache clinics in 4 different hospitals around the country that fulfill the following criteria: history of frequent headache (over 15 days a month) in the first consultation and follow-up of at least 1 year in the headache clinic.

For each patient, the following items were available: clinical diagnosis, treatment received, paraclinical studies performed, disability scale (MIDAS—migraine disability assessment), quality-of-life scale (SF-36), and a satisfaction questionnaire. The patients were classified using the International Classification of Headache Disorders-II.

For the analysis, we compared the patient’s situation at the first consultation with the results after a 1-year follow-up and treatment in the headache clinics.

RESULTS
Thirty patients were included in this pilot study, 4 of which were male and 26 were female. The mean age was 46 years (19 to 64). On average, their headache frequency was 26 days/month (19 to 30) and their primary headaches had lasted 17 years (2 to 26).

The diagnosis was chronic tension-type headache (TTH) in 8 cases, migraine in 3 cases, and migraine and TTH in 21 cases. A total of 22 patients were overusing medication.

The average number of previous consultations related with the headaches was 8.3 (3 to 18). During the first year of follow-up in the headache clinics, the average of consultations, including the initial evaluation, was 4.3.

The majority of patients (80%) were physician referred and the other came from the emergency department and other health professionals. All were unsatisfied or very unsatisfied with the assistance received previously.

Only 30% of patients had received preventive treatment before attending our clinics and triptans had been prescribed in only 10%, in a population where over 70% were severe migraineurs.

After 1 year of treatment in our clinics, the headache frequency was reduced in more than 50% in 80% of the patients and in more than 25% in 86% of patients. A total of 90% of the overusers of symptomatic medication reduced their consumption below the overuse level. On average their headache frequency was reduced to 9.3 days/month (range: 1 to 30). These results strongly correlated with changes in the disability and quality-of-life scales. The mean MIDAS score was reduced significantly from 81 to 28; there was a patient that changed from 210 to 4. The quality of life improved in all domains of the SF-36 and significantly in mental health, social functioning, pain, and physical role. Finally, 92% of patients were satisfied or very satisfied with the treatment (none declared to be satisfied in the first consultation; Fig.).

COMMENTS
This pilot study shows that headache units are efficient in treatment of headache patients, even in difficult cases, as they offer a high degree of clinical improvement, satisfaction, and important benefits regarding disability and quality of life. The study has limitations because it is a pilot study, but the population is representative of the patients with frequent headaches attending headache clinics. Some people can argue that the patients could receive different treatments because they were treated in different clinics; in our opinion, this is an advantage because it allows us to measure the efficacy of the structure independently of the place. Other concern could be that we are not comparing our group to nontreated patients or patients treated in other clinical settings such as primary care, but most of them had been treated before at the primary care level, and the number of previous consultations for headache was high. The treated group consisted of patients who failed to improve with standard therapy and had a very long history of headache.

We have shown that the clinical improvement with a reduction in headache frequency in more than 80% of patients, and a significant reduction of medication overuse up to 90%, correlates with a spectacular reduction of disability and with an important improvement in quality of life. This success was very well recognized by these patients, as 92% of them were satisfied or very satisfied after attending the headache clinic during a year.

With these results, this concept seems to be cost-effective for the society, but in the future studies it should be necessary to include measures of direct and, especially,
indirect costs, which could be highly reduced with a specialized practice.\textsuperscript{4} It should also be important to analyze within a larger number of patients whether certain subgroups such as refractory patients would improve more in a tertiary center, as has been suggested for posttraumatic headaches.\textsuperscript{5}

In conclusion, with these data, coming from the clinical practice, we show some evidence that tertiary headache centers are useful for patients and society. However, there is very little scientific evidence on the cost-effectiveness of this specialized care in the headache field. Our results call for future studies analyzing these points, which could serve to convince health authorities on the necessity and usefulness of headache clinics.

\textit{Conflicts of Interest:} None

\textbf{REFERENCES}


