

- 4 Dautzenberg B, Piperno D, Diot P, Truffot-Pernot C, Chauvin JP. Clarithromycin in the treatment of *Mycobacterium avium* lung infections in patients without AIDS. Clarithromycin Study Group of France. *Chest* 1995;**107**:1035–40
- 5 Roussel G, Igual J. Clarithromycin with minocycline and clofazimine for *Mycobacterium avium* intracellulare complex lung disease in patients without the acquired immune deficiency syndrome. GETIM. Groupe d'Etude et de Traitement des Infections a Mycobacteries. *Int J Tuberc Lung Dis* 1998;**2**:462–70
- 6 Uzun C, Koten M, Adali MK, Yorulmaz F, Yagiz R, Karasalioglu AR. Reversible ototoxic effect of azithromycin and clarithromycin on transiently evoked otoacoustic emissions in guinea pigs. *J Laryngol Otol* 2001;**115**:622–8
- 7 Kolkman W, Groeneveld JH, Baur HJ, Verschuur HP. Ototoxicity induced by clarithromycin [in Dutch]. *Ned Tijdschr Geneeskde* 2002;**146**:1743–5
- 8 Dokmeci I. *Pharmacology: Basic concepts* [in Turkish]. Istanbul: Nobel Tip Kitapevleri, 2000
- 9 Brummett RE. Ototoxic liability of erythromycin and analogues. *Otolaryngol Clin North Am* 1993;**26**:811–9
- 10 Dylewski J. Irreversible sensorineural hearing loss due to erythromycin. *CMAJ* 1988;**139**:230–1
- 11 Röss BD, Gross EM. Irreversible sensorineural hearing loss as a result of azithromycin ototoxicity. A case report. *Ann Otol Rhinol Laryngol* 2000;**109**:435–7
- 12 Levin G, Behrendt E. Irreversible ototoxic effect of erythromycin. *Scand Audiol* 1986;**15**:41–2

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### **Cholesterol granuloma of the frontal sinus**

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Dear Sirs,

We read with interest the case report by Shykhon *et al.* on Cholesterol granuloma of the frontal sinus.<sup>1</sup> Cholesterol granuloma is indeed far less commonly found in the paranasal sinuses than the temporal bone, with the frontal sinus being less frequently affected than the maxillary sinus. Our own unpublished series of five frontal sinus cholesterol granulomas over a ten-year period in a specialist Rhinology unit reflects the rarity of this condition. As the paper indicates, most of the literature on the subject concerns the petrous temporal bone, or, in the para-nasal sinuses, the maxillary sinus. It is of significance, however, that while the authors state “few cases have been reported” in the frontal sinus, they fail to cite any of the publications reporting this condition in the medical literature, including a previous article in the *Journal of Laryngology and Otolology*.<sup>2</sup>

The lesion, which may follow a history of trauma, originates within the diploe of the frontal bone from where it expands extra-periosteally around the orbit. It is not surprising therefore that affected patients usually present to an Ophthalmologist. Our Medline search on cholesterol granuloma of the frontal sinus from 1974 to 2002 identified that the largest published series was from Moorfields Eye Hospital, who described 27 cases of orbito-frontal cholesterol

granuloma seen between 1967 and 1988.<sup>3</sup> All but one of the patients presented with expansion of the lesion into the extra-periosteal space in the region of the lacrimal fossa. Six of the 29 patients had a history of trauma to the area and the authors suggested that haemorrhage into the diploe of the frontal bone was the most likely cause. All patients were cured by extra-periosteal drainage. The radiological findings of 31 patients from the same unit from 1974 to 1991 were published in 1992.<sup>4</sup> All patients had been investigated by plain X-ray, 21 underwent CT imaging and one patient an MRI study. The typical CT findings of ragged bony destruction with a soft tissue mass no more dense than brain extending extra-periosteally into the orbit are discussed, together with the findings of high signal intensity on both the T1 and T2 images of the MRI scan. Very similar radiological findings were described in a report of 11 patients from Holland.<sup>5</sup>

Our Midline literature search on ‘cholesterol granuloma’ from 1966 to the present day identified 421 reports in total, 30 of which detailed the clinical, pathological or radiological features of between one and 31 patients with disease in the orbito-frontal region. The condition is clearly not as rarely reported as Shykhon *et al.* suggest and we feel that their paper would have benefited from a more comprehensive assessment of the current literature than was evidently performed.

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### **References**

- 1 Shykhon SE, Trotter MI, Morgan DW, Reuser TTQ, Henderson MJ. Cholesterol granuloma of the frontal sinus. *J Laryngol Otol* 2002;**116**:1041–3
- 2 Butler S, Grossenbacher R. Cholesterol granuloma of the paranasal sinuses. *J Laryngol Otol* 1989;**103**:776–9
- 3 McNab AA, Wright JE. Orbitofrontal cholesterol granuloma. *Ophthalmology* 1990;**97**:28–32
- 4 Rowland Hill CA, Moseley IF. Imaging of orbitofrontal cholesterol granuloma. *Clin Radiol* 1992;**46**:237–42
- 5 Eijpe AA, Koornneef L, Verbeeten B Jr, Peeters FL, Zonneveld FW. Cholesterol granuloma of the frontal bone: CT diagnosis. *J Comput Assist Tomogr* 1990;**14**:914–7

### **Analytical and clinical evaluation of CYFRA 21-1 by electrochemiluminescent immunoassay in head and neck squamous cell carcinoma. *JLO* 2003;**117**:190–4**

Dear Sirs,

While we took note of the investigation performed by Deng *et al.*<sup>1</sup> with great interest, we would like to state the following comments:

The clinical importance of the Cyfra 21-1 serum concentration as tumour marker in patients with squamous cell carcinomas of the head and neck has been described previously.<sup>2–4</sup> In a recent publication<sup>4</sup> the Cyfra 21-1 serum concentration is evaluated by means of an ELISA test kit. Deng

*et al.*<sup>1</sup> used a new electrochemiluminescent immunoassay (ECLIA) for Cyfra 21-1 measurements in the serum of patients with squamous cell carcinomas of the head and neck. The advantages, or maybe also disadvantages, of the new ECLIA in contrast to the well accepted ELISA for determination of the Cyfra 21-1 serum concentration are not discussed by the authors, apart from the remark that the sensitivity of ECLIA seems to be slightly higher. ELISA is a rapid, sensitive, and reproducible technique, as well. Since with ECLIA a new technique is described, more detailed information concerning the performance of the test would be appropriate.

As mentioned previously,<sup>5</sup> no survival analysis should be performed with patients suffering from squamous cell carcinomas of different tumour sites in the head and neck area, because the survival probability per se strongly depends on the tumour site. This might explain the lack of statistical significance in the difference between the Cyfra 21-1 positive and the Cyfra 21-1 negative group, described by Deng *et al.*<sup>1</sup>

In conformity with Deng *et al.*,<sup>1</sup> an increase of the Cyfra 21-1 serum concentration in case of disease progression, in terms of residual tumour progression, recurrency, and especially in terms of appearance of distant metastasis has previously been described. Also, a decrease of the Cyfra 21-1-serum concentration after therapy in patients with squamous cell carcinomas of the head and neck has been seen earlier.<sup>4</sup> Cyfra 21-1 is a well accepted tumour marker in non-small-cell lung cancer.<sup>6</sup> The controversy about the usefulness of Cyfra 21-1 as serum tumour marker in head and neck squamous cell carcinomas is probably due to difficulties to find the appropriate cut-off level.<sup>7</sup> Cyfra 21-1 serum levels in patients with head and neck cancer are generally lower than in patients with lung cancer and they are often even equivalent to levels which are considered normal in lung cancer patients. Additionally, a wide range of Cyfra 21-1 serum levels were observed in patients at the time of primary tumour diagnosis.<sup>2,4</sup> Also, the Cyfra 21-1 serum levels vary widely in healthy persons.<sup>8,9</sup> Cytokeratins are not organ specific, and they appear in all epithelial tumours, as well as in normal epithelium. This is a limitation on the tumour marker potential of Cyfra 21-1.<sup>10,11</sup>

In conclusion, the Cyfra 21-1 serum concentration is not a suitable tumour marker for diagnosis of squamous cell carcinomas of the head and neck, but an increase of Cyfra 21-1 in serial measurements indicates impending disease progression in the individual patient. Therefore, the Cyfra 21-1 serum concentration is a good marker for follow-up in patients with squamous cell carcinoma of the head and neck, and in case of an upward trend of Cyfra 21-1 in the serum, staging procedures are recommended.

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#### References

- Deng YF, Chen P, Lin YZ, Le JZ, Wu XL, Yu MQ, *et al.* Analytical and clinical evaluation of CYFRA 21-1 by electrochemiluminescent immunoassay in head and neck squamous cell carcinoma. *J Laryngol Otol* 2003;**117**:190–4
- Doweck I, Barak M, Greenberg E, Uri N, Kellner J, Lurie M, *et al.* Cyfra 21-1. A new potential tumor marker for squamous cell carcinoma of head and neck. *Arch Otolaryngol Head Neck Surg* 1995;**121**:177–181
- Maass JD, Hoffmann-Fazel A, Goeroegh T, Hoffmann M, Meyer J, Gottschlich S, *et al.* Cyfra 21-1: A serological help for detection of distant metastases in head and neck cancer. *Anticancer Res* 2000;**20**:2241–4
- Kuropkat C, Lippert BM, Werner JA. Follow-up with Cyfra 21-1 in patients with squamous cell carcinomas of the head and neck. *Oncology* 2002;**63**:280–5
- Kuropkat C, Rudolph P, Frahm SO, Parwaresch R, Werner JA. Proliferation marker Ki-S11 – a prognostic indicator for squamous cell carcinoma of the hypopharynx. *Virchows Arch* 1999;**435**:590–5
- Rastel D, Ramaioli A, Cornille F, Thirion B. Cyfra 21-1, a sensitive and specific new tumor marker for squamous cell lung cancer: Report of the first European Multicenter Evaluation. *Eur J Cancer* 1994;**30A**:601–6
- Niemann AM, Goeroegh T, Gottschlich S, Lippert BM, Werner JA. Cut-off value determination of Cyfra 21-1 for squamous cell carcinoma of the head and neck. *Anticancer Res* 1997;**17**:2859–60
- Yen TC, Lin WC, Kao CH, Cheng KY, Wang SJ. A study of a new tumour marker, Cyfra 21-1, in squamous cell carcinoma of the head and neck, and comparison with squamous cell carcinoma antigen. *Clin Otolaryngol* 1998;**23**:82–6
- Lee JK, Hsieh JF, Tsai SC, Ho YJ, Sun SS, Kao CH. Comparison of Cyfra 21-1 and squamous cell carcinoma antigen in detecting nasopharyngeal carcinoma. *Ann Otol Rhinol Laryngol* 2001;**110**:775–8
- Franke WW, Schmid E, Osborn M, Weber K. Different intermediate-sized filaments distinguished by immunofluorescence microscopy. *Proc Natl Acad Sci USA* 1978;**75**:5034–8
- Bongers V, Braakhuis BJM, Snow GB. Circulating fragments of cytokeratin 19 in patients with head and neck squamous cell carcinoma. *Clin Otolaryngol* 1995;**20**:479–82

#### Author's reply

Dear Sirs,

We thank Dr Kuropkat for the comments on our paper.<sup>1</sup>

Up to now, the CYFRA 21-1 serum concentration was measured using a dot-blot assay, IRMA, ELISA, and ECLIA. In our study, we utilized ECLIA. ECLIA is a new method for the determination of cytokeratin 19(CYFRA 21-1) in the Elecsys 2010 immunoassay system. It provides a new noninvasive adjunct to test the CYFRA 21-1 concentration of human serum, tissue fluid and urine. We introduce it as follows:

#### Elecsys 2010 system

The Elecsys® 2010 analyser [Boehringer Mannheim (BM)] is based on the ability of the electrochemiluminescent label molecule, a tris (2,2'-bipyridyl)-ruthenium (II) complex, to be repeatedly excited by tripropylamine, thus leading to an amplification of