especially the case, if the screening program has been implemented region-wise, because it is then possible to identify a comparison group not yet invited to screening. However, screening changes the age-specific incidence in cohorts of women offered screening. This includes a prevalence peak at first screen; an artificial aging at subsequent screens; and a compensatory dip after end of screening [5,6]. Therefore, studies of overdiagnosis require also that women can be followed for a sufficiently long period after end of screening for the compensatory dip to materialize. Such studies have been undertaken in for instance Florence Italy [16]; in Finland [17]; and in Denmark [18].

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

References

[1] Welch HG, Prorok PC, O'malley AJ, et al. Breast-cancer tumor size, overdiagnosis, and mammography screening effectiveness. N Engl J Med. 2016;375:1438–1447.

[2] Ballard-Barbash R, Griffin MR, Wold LE, et al. Breast cancer in residents of Rochester, Minnesota: incidence and survival, 1935 to 1982. Mayo Clin Proc. 1987;62:192–198.

[3] Glass AG, Hoover RN. Rising incidence of breast cancer: relationship to stage and receptor status. J Natl Cancer Inst. 1990;82:693–696.

[4] Holford TR, Roush GC, McKay LA. Trends in female breast cancer in Connecticut and the United States. J Clin Epidemiol. 1991;44:29–39.

[5] Boer R, Warmerdam P, de Koning H, et al. Extra incidence caused by mammographic screening. Lancet. 1994;343:979.

[6] Duffy SW, Lynge E, Jonsson H, et al. Complexities in the estimation of overdiagnosis in breast cancer screening. Br J Cancer. 2008;99:1176–1178.

[7] Zheng T, Holford TR, Chen Y, et al. Time trend of female breast carcinoma in situ by race and histology in Connecticut, U.S.A. Eur J Cancer. 1997;33:96–100.

[8] NORDCAN [Internet]; [cited 2017 Jan 17]. Available from: http://www-dep.iarc.fr/NORDCAN/English/frame.asp

[9] Clemmesen J, Stancke B. The effects of an anti-cancer campaign. Ugeskr Laeg. 1964;126:1564–1565.

[10] Rostgaard K, Væth M, Rootzén H, et al. Why did the breast cancer lymph node status distribution improve in Denmark in the pre-mammography screening period of 1978–1994? Acta Oncol. 2010;49:313–321.

[11] Jensen A, Olsen AH, von Euler-Chelpin M, et al. Do nonattenders in mammography screening programmes seek mammography elsewhere? Int J Cancer. 2005;113:464–470.

[12] Olsen AH, Njor SH, Vejborg I, et al. Breast cancer mortality in Copenhagen after introduction of mammography screening: cohort study. BMJ. 2005;330:220.

[13] Njor SH, Schwartz W, Blichert-Toft M, et al. Decline in breast cancer mortality: how much is attributable to screening? J Med Screen. 2015;22:20–27.

[14] Utzon-Frank N, Vejborg I, von Euler-Chelpin M, et al. Balancing sensitivity and specificity: sixteen year's of experience from the mammography screening programme in Copenhagen, Denmark. Cancer Epidemiol. 2011;35:393–398.

[15] Dansk Kvalitetsdatabase for Brystkræftscreening. Danish Quality database for breast cancer screening. Annual report 2010, first national screening round, Denmark; 2011 [Internet]; [cited 2017 Jan 17]. Available from: http://www.kcks-vest.dk/siteassets/de-kliniske-databaser/mammografiscreening/arsrapport-dkms-2010.pdf

[16] Puliti D, Zappa M, Miccinesi G, et al. An estimate of overdiagnosis 15 years after the start of mammographic screening in Florence. Eur J Cancer. 2009;45:3166–3171.

[17] Heinävaara S, Sarkeala T, Anttila A. Overdiagnosis due to breast cancer screening: updated estimates of the Helsinki service study in Finland. Br J Cancer. 2014;111:1463–1468.

[18] Njor SH, Olsen AH, Blichert-Toft M, et al. Overdiagnosis in screening mammography in Denmark: population based cohort study. BMJ. 2013;346:f1064.

LETTER TO THE EDITOR

A case of isolated small cell carcinoma of the brain

C. Noonan[a] and M. James[a,b]

[a]Department of Oncology, Canterbury District Health Board, Christchurch, New Zealand; [b]Department of Medicine, University of Otago, Christchurch, New Zealand

Case description

Presentation

A 43-year-old Caucasian female presented to the emergency department with a four week history of decreased fluency of speech and headache. She had no significant previous medical history or regular medications, although was a current cigarette smoker with 20 pack-year history. On examination, she had expressive dysphasia, global right-sided hypoesthesia, hypertonicity and weakness of the right upper limb.

Investigation

Her initial MR brain revealed prominent rim-enhancing neoplasms to the left parietal (41 mm AP × 35mm T) and posteromedial temporal lobes (25 mm AP × 11 mm T) with associated mass effect (as shown in Figure 1). A provisional diagnosis of brain metastases from an unknown primary was made. Staging investigations (including CT, MR and FDG PET-CT modalities) showed no evidence of extra-cranial disease. Serum haematology, biochemistry and tumour markers

CONTACT Charles Noonan charlienoonan@gmail.com Oncology Department, Christchurch Hospital, Canterbury, New Zealand

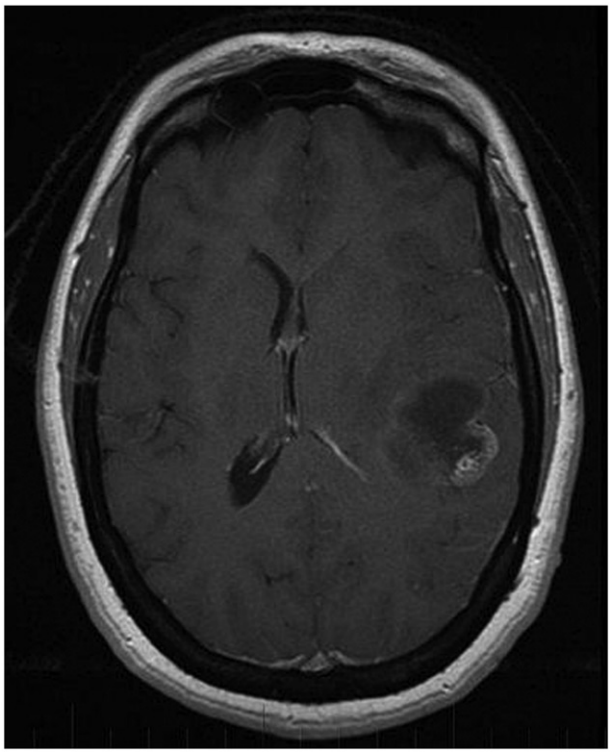

Figure 1. Initial presentation MR brain.

(including chromogramin A) were unremarkable. Further investigation including colonoscopy, nuclear medicine bone scan, ovarian ultrasound, breast ultrasound and mammography failed to demonstrate extra-cranial disease.

Diagnosis

The patient underwent a left parietal craniotomy with en-bloc resection of the larger tumour mass in the left parietal region. She recovered well post-operatively with mild residual expressive dysphasia.

On histopathological analysis, the tumour was composed of sheets of cohesive epithelial cells with a high nuclear:cytoplasmic ratio, nuclear hyperchromasia, pleomorphism, a high mitotic rate and minimal eosinophilic cytoplasm. There were areas that showed prominent nuclear moulding, and cells were arranged around fibrovascular cores, with palisading of nuclei. The malignant cells were positive for pancytokeratin, EMA, CK7, TTF-1, villin, CEA and weakly for CA125. They were negative for CK20, CK5/6, vimentin, GFAP, S100, thyroglobulin and GCDFP. Additional staining showed strong and diffusely positive staining CD56 and chromogranin A, and negative staining for synaptophysin.

The findings above are diagnostic of a poorly differentiated neuroendocrine (small cell) carcinoma. Immunohistochemical profiling and electron microscopy findings were suggestive of a lung primary, however, further compatible extra-pulmonary sites included the renal tract and cervix (also expressing TTF-1 positivity). The pathology was externally reviewed and validated by an independent pathologist.

A diagnosis of small cell cancer of unknown primary (SCUP) with metastases to the brain was made.

Treatment

She subsequently underwent whole brain radiotherapy to a dose of 30 gray administered in 15 treatments. This was followed by a second phase 'boost' delivering 10 gray in five treatments to known disease within the left parietal lobe. No systemic treatment was administered.

The patient remained well for three years following radiotherapy treatment before developing right facial and left arm paraesthesia. A re-staging MR brain identified two new lesions in the right frontal and insular lobes. Given the localised nature of the recurrent disease, stereotactic radiotherapy was given with a single dose of 14 gray.

Despite this, the lesions progressed over the following six months. A second craniotomy involving resection of the symptomatic right frontal lobe lesion was performed, and her symptoms improved. Histologic examination and immunohistochemistry confirmed recurrent neuroendocrine (small cell) carcinoma.

Serial imaging (CT, MR, FDG PET-CT) over the subsequent five years has not revealed evidence of extra-cranial disease. Aside from residual left upper limb weakness and expressive dysphasia, the patient remains systemically well.

Discussion

Neuroendocrine tumours (NETs) are a heterogeneous group of neoplasms arising from cells of the endocrine (hormonal) and nervous systems [1,2]. Although considered collectively, they differ in histological appearance, biological behaviour and sensitivity to treatment. The annual incidence of clinically significant NETs is estimated as 2.5–5 per 100,000; although the prevalence of silent and other undetected tumours is likely higher [3,4].

A distinct class of poorly differentiated NETs are small cell (oat-cell) tumours. The vast majority of small cell carcinomas arise in lung tissue (SCLC), while less common extra-pulmonary small cell carcinoma (EPSCC) sites include thyroid, prostate, urinary bladder, skin, female genital tract, larynx, salivary glands and gastrointestinal tissues [5]. Extra-pulmonary tumour outside these sites is classed as small cell carcinoma of unknown primary (SCUP), and represent only 1–2% of all small cell carcinomas. This diagnosis typically precedes subsequent identification of primary disease [5,6].

Small cell carcinomas are characterised histologically by their short doubling time, scant cytoplasm, flat shape, high growth fraction; and biologically by their aggressive nature and early development of metastatic disease. As in this case, immunohistochemistry is increasingly utilised to confirm the diagnosis of small cell carcinoma; characteristically staining positive for chromogranin A, neuron-specific enolase (NSE), and/or synaptophysin. When discriminating between lung and extra-pulmonary disease, expression of thyroid transcription factor 1 (TTF1) may be helpful, but it lacks the sensitivity to distinguish between primary and metastatic lesions [7]. Cytogenetic analysis has shown promise in differentiating between lung and extra-pulmonary disease; with loss of

chromosome 10q and deletions in chromosome 13 recently emphasised in pulmonary origin disease [8]. However, currently there is no accepted cytogenetic pattern that definitively distinguishes between primary and metastatic, or pulmonary and EPSCC.

Prognosis for patients with SCUP varies widely from months to several years; dependent on the anatomical location, extent of disease, and response to treatment. A recent large retrospective study ($N = 120$) reported median survival for patients for limited versus extensive disease as 1.4 years and 0.7 years, respectively [9]. Another retrospective analysis ($N = 101$) reported median survival for patients with SCUP as 2.5 months [5]. Given their rare incidence, treatment recommendations for EPSCC and SCUP are largely derived from single-centre experiences or extrapolated from small cell lung cancer studies [9]. However, given the known differences in aetiology, clinical course and survival between SCLC and SCUP/EPSCC, many clinicians argue a differential approach. Recent evidence increasingly favours the targeted use of loco-regional therapies such as surgery and radiotherapy as these may provide prolonged disease-free survival for patients with limited EPSCC [10]. This is in contrast to small cell lung cancer (SCLC), which is largely considered a systemic disease and rarely amenable to localised therapies at time of diagnosis [11–13].

SCUP isolated to the central nervous system without evidence of further disease remains extremely rare, and few case reports exist to our knowledge [14,15]. Chionh et al. reported two cases of solitary intra-cranial small cell carcinoma with no further disease on staging investigations [15]. Initial treatment involved primary surgical resection and whole brain radiotherapy (30 gray delivered in 10 treatments). Both patients later developed recurrent CNS disease. Additional radiotherapy was administered to affected spinal sites (30 gray in 10 treatments), followed by carboplatin (AUC 5, day 1) and etoposide (120 mg/m^2, days 1–3). At the time of publication, one patient had completed four cycles of chemotherapy and was disease-free at 33 months from diagnosis. The second had died of an acute myocardial infarction shortly after the first cycle of etoposide. Combined with our own experience, these cases support the role of aggressive local therapies in providing prolonged local control and recurrence-free survival.

Given the rarity of SCUP isolated to the brain, we initially assumed the patient's tumour represented metastatic disease from a lung primary (SCLC). However, this assumption was countered by the absence of distant disease on serial FDG PET-CT, MR and CT imaging. Several similar cases are reported in the literature describing incidences where primary lesions have undergone spontaneous regression, or where a primary tumour has undergone early metastasis, and metastases have subsequently mutated to select for more rapid proliferation [5,6].

This case study describes a very rare presentation of isolated CNS small cell carcinoma; which may represent either SCUP metastasised to the brain, or primary small cell carcinoma of the brain. The patient was observed for five years without detection of distant primary or extra-cranial disease and displayed a relatively indolent clinical course. It supports the use of loco-regional therapies such as surgery and radiotherapy in the treatment of similar patients.

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The submitted report was performed in accordance with appropriate ethical standards. Consent was granted from the patient for use of history, imaging and laboratory results utilised in this case report. Written informed consent was provided by the patient for publication in a scientific journal.

Disclosure statement

The authors report no conflicts of interest or competing interests.

References

[1] Mavrakis AN, Halpern EF, Barker FG, 2nd, et al. Diagnostic evaluation of patients with a brain mass as the presenting manifestation of cancer. Neurology. 2005;65:908–911.
[2] Wong E. Clinical presentation and diagnosis of brain tumors. In: Eicher A, editor. UpToDate. Waltham (MA): UpToDate; 2016.
[3] Klimstra DS, Modlin IR, Coppola D, et al. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. Pancreas. 2010;39:707–712.
[4] Oberg K, Castellano D. Current knowledge on diagnosis and staging of neuroendocrine tumors. Cancer Metastasis Rev. 2011;30:3–7.
[5] Haider K, Shahid RK, Finch D, et al. Extrapulmonary small cell cancer: a Canadian province's experience. Cancer. 2006;107:2262–2269.
[6] Lobins R, Floyd J. Small cell carcinoma of unknown primary. Semin Oncol. 2007;34:39–42.
[7] Chhieng DC, Cangiarella JF, Zakowski MF, et al. Use of thyroid transcription factor 1, PE-10, and cytokeratins 7 and 20 in discriminating between primary lung carcinomas and metastatic lesions in fine-needle aspiration biopsy specimens. Cancer. 2001;93:330–336.
[8] Testa JR, Liu Z, Feder M, et al. Advances in the analysis of chromosome alterations in human lung carcinomas. Cancer Genet Cytogenet. 1997;95:20–32.
[9] Brennan SM, Gregory DL, Stillie A, et al. Should extrapulmonary small cell cancer be managed like small cell lung cancer? Cancer. 2010;116:888–895.
[10] Walenkamp AM, Sonke GS, Sleijfer DT. Clinical and therapeutic aspects of extrapulmonary small cell carcinoma. Cancer Treat Rev. 2009;35:228–236.
[11] Remick SC, Ruckdeschel JC. Extrapulmonary and pulmonary small-cell carcinoma: tumor biology, therapy, and outcome. Med Pediatr Oncol. 1992;20:89–99.
[12] Hainsworth JD, Johnson DH, Greco FA. Poorly differentiated neuroendocrine carcinoma of unknown primary site. A newly recognized clinicopathologic entity. Ann Intern Med. 1988;109:364–371.
[13] Hu C, Chang EL, Hassenbusch SJ III, et al. Nonsmall cell lung cancer presenting with synchronous solitary brain metastasis. Cancer. 2006;106:1998–2004.
[14] Terada T. Small cell carcinoma of the brain without extracranial involvement by serial CT, MRI and PET. Int J Clin Exp Pathol. 2010;3:323–327.
[15] Chionh F, Azad A, Lee C. Small cell carcinoma of unknown primary presenting with disease confined to the central nervous system. Acta Oncol. 2009;48:317–318.