On the other hand, PD-L1 expression in the TB microenvironment was rapidly down-regulated once the infection was under control despite the presence of lung cancer. The expression of PD-L1 seemed to proceed by each disease course without significant interaction and to not be influenced by steroid or immune checkpoint inhibitor treatment.

Our patient proved the theory of a hypersensitivity response to TB reactivation with pericardial tamponade after immune checkpoint inhibition. There is no interaction of the expression of PD-L1 between lung cancer and TB when the two diseases coexist. We suggest that tuberculous serositis be included in the differential diagnosis when new effusion develops in patients with lung cancer who have been receiving immune checkpoint inhibitors.

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References

1. Reungwetwattana T, Adjei AA. Anti-PD-1 antibody treatment and the development of acute pulmonary tuberculosis. *J Thorac Oncol*. 2016;11:2048–2050.
2. Fujita K, Terashima T, Mio T. Anti-PD1 antibody treatment and the development of acute pulmonary tuberculosis. *J Thorac Oncol*. 2016;11:2238–2240.
3. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*. 2012;12:252–264.
4. Jurado JO, Alvarez IB, Pasquinelli V, et al. Programmed death (PD)-1:PD-ligand 1/PD-ligand 2 pathway inhibits T cell effector functions during human tuberculosis. *J Immunol*. 2008;181:116–125.
5. Ellner JJ, Barnes PF, Wallis RS, Modlin RL. The immunology of tuberculous pleurisy. *Semin Respir Infect*. 1988;3:335–342.
6. Wherry EJ. T cell exhaustion. *Nat Immunol*. 2011;12:492–499.

Numb Chin Syndrome: An Ominous Sign of Lung Cancer

To the Editor:

We report the case of an 84-year-old man with a heavy smoking history and a 1-month history of hoarseness and progressive productive cough. Radiological screening showed a left upper lung mass, and stage 4 SCLC (cT3N2N1b, extensive disease) with pulmonary and bone metastases was subsequently diagnosed. As first-line chemotherapy, carboplatin/etoposide was administered in May 2016. In addition, denosumab was administered every 4 weeks to control the iliac bone metastasis. After four courses of chemotherapy, his symptoms and chest radiological findings improved significantly, resulting in partial remission. However, he reported partial paresthesia of the right mandible since July 2016 and was referred to the dental clinic of our hospital. His paresthesia was localized to the tip of the right chin, lip, and gingiva, without tongue dysfunction. We suspected medication-related osteonecrosis of the jaw, and therefore discontinued the denosumab treatment. Oral cleaning with various antibiotics was conducted. However, the

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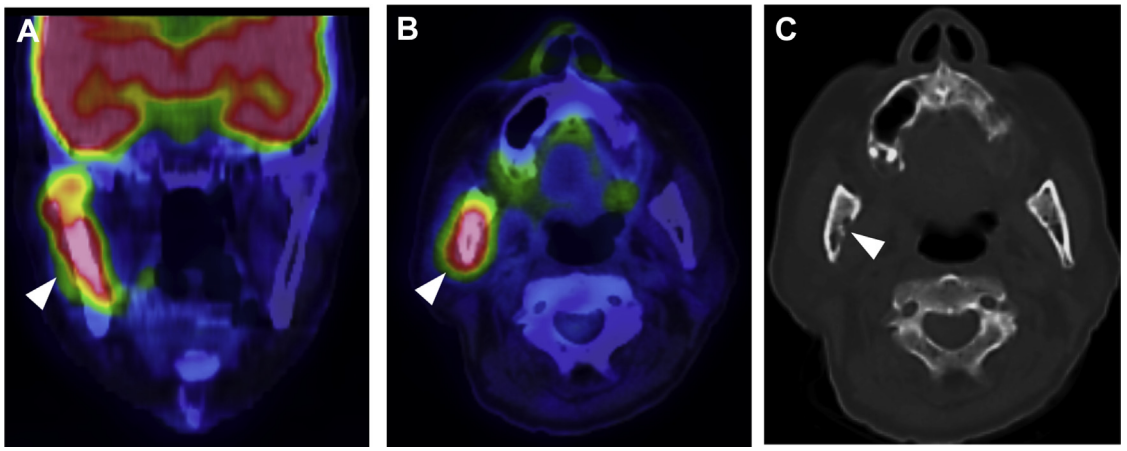

Figure 1. Positron emission tomography and computed tomography findings for an 84-year-old man who presented with hoarseness and cough. Both coronal (*A*) and transverse (*B*) images from the positron emission tomography scan show a fluorodeoxyglucose-avid lesion in the right side of the jaw (*arrowheads*), and the computed tomography scan (*C*) shows an osteolytic lesion (*arrowhead*).

patient experienced pain in the right side of the jaw, which gradually restricted mouth opening. In January 2017, positron emission and computed tomography confirmed a fluorodeoxyglucose-avid osteolytic lesion in the right mandible (Fig. 1*A–C*). A right mandible biopsy revealed the presence of SCLC cells, indicating that this was a new metastatic bone lesion. Numb chin syndrome (NCS) due to injury of the inferior alveolar nerve by the metastatic lesion around the right mandibular angle was diagnosed (Fig. 2*A*). At this point, the patient's right mandible showed swelling, which resulted in him drooling because of masseter muscle dysfunction. On the basis of a diagnosis of SCLC progression, we administered second-line treatment with amrubicin, which resulted in partial remission of the symptoms.

NCS (also known as mental nerve neuropathy or Roger's sign[1]) is a pure sensory neuropathy that manifests as numbness of the chin in the distribution of the mental nerve.[2] Although Calverley and Mohnac[3] first reported five patients with chin numbness due to various malignancies in 1963, the famous neurologist Charles Bell had already reported this symptom in a patient with breast cancer in 1830.[4] This well-known but relatively rare syndrome has various causes, ranging from benign disease (such as infection, trauma, diabetes mellitus, amyloidosis, and vasculitis) to malignant disease (such as breast cancer, lymphoma, and lung cancer); however, until proven otherwise, we recommend considering this sign to be malignancy associated. Pathologically, NCS is thought to be caused by two mechanisms: (1) damage of the trigeminal nerve and its branches (direct nerve compression by bone metastasis or neural invasion (Fig. 2*B*) or (2) damage of the central nervous system (brain metastasis or basal skull and leptomeningeal dissemination). The recent introduction of zoledronic acid or denosumab for bone metastasis has made the diagnosis of NCS more complex, because these drugs can cause medication-related osteonecrosis of the jaw,[5] which mimics NCS. However, the treatment for the two diseases is completely different. It is

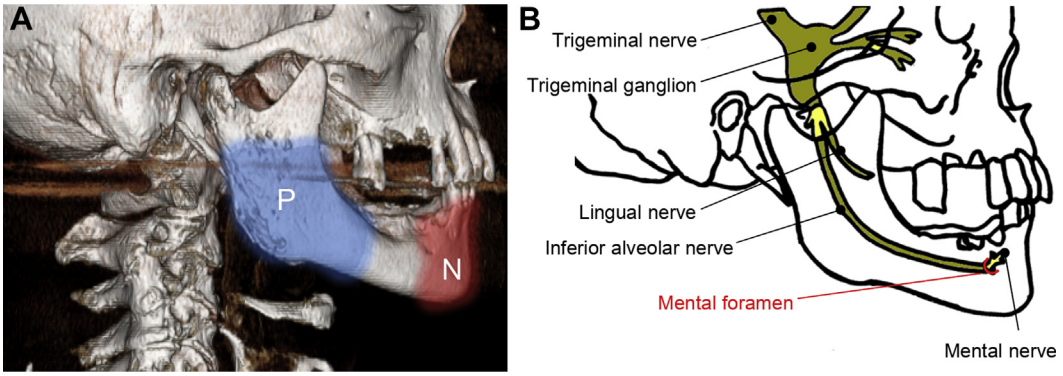

Figure 2. Schematic images of the symptoms and associated nerves. (*A*) The patient's symptoms were plotted on the computed tomography–derived reconstructed three-dimensional image. (*B*) Distribution of the trigeminal nerve and its branches (inferior alveolar nerve and mental nerve). Abbreviations: N, numbness; P, pain.

important for clinicians to consider NCS as a rare but important ominous sign in patients with lung cancer.

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References

1. Roger H, Pallais J. Le signe du mentonnier (paresthesie et anesthesie unilaterale) revelateur d'un processus metastatique. *Rev Neurol*. 1937;2:751–752.
2. Laurencet FM, Anchisi S, Tullen E, Dietrich PY. Mental neuropathy: report of five cases and review of the literature. *Crit Rev Oncol Hematol*. 2000;34:71–79.
3. Calverley JR, Mohnac AM. Syndrome of the numb chin. *Arch Intern Med*. 1963;112:819–821.
4. Furukawa T. Charles Bell's description of numb chin syndrome. *Neurology*. 1988;38:331.
5. Ruggiero SL, Dodson TB, Fantasia J, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw-2014 update. *J Oral Maxillofac Surg*. 2014;72:1938–1956.

FISH Analysis of Crizotinib Target Genes *ROS1/ALK/MET* in Malignant Mesothelioma

To the Editor:

Malignant mesothelioma (MM) is a particularly aggressive tumor in which, despite advances in chemotherapy, radiation therapy, and surgical management, the prognosis remains poor and median survival tends to be 1 year after diagnosis.[1] A breakthrough in the treatment of MM could be the targeted therapy already successfully used in other cancers. In this regard, early promising antitumor activity has been reported for the oral multitargeted tyrosine kinases inhibitor (TKI) crizotinib.

Crizotinib is currently used for the treatment of advanced NSCLC showing *ROS1* rearrangement, anaplastic lymphoma receptor tyrosine kinase gene (*ALK)* rearrangement or MMNG HOS Transforming gene (*MET*) amplification.[2]

In our previous letter of January 2016 in the *Journal of Thoracic Oncology*[3] we reported the fluorescence in situ hybridization analysis of *MET* gene copy number in MM showing amplification in about 2% and high polysomy in 6.7% of patients. We concluded that this set of patients might be candidates for treatment with anti–mesenchymal-to-epithelial transition TKIs, including crizotinib.

In the present Letter to the Editor, to verify the number of patients with MM who could potentially benefit from treatment with crizotinib, we have also analyzed the status of the *ROS1* and *ALK* genes. Furthermore, we have expanded the series of patients with MM analyzed for the status of *MET*.

This study was approved by the Liguria Region Ethics Committee (P.R. 207REG2014), and written informed consent was obtained from all patients. We analyzed 106 MM samples from various tissues (60 epithelioid, 34 sarcomatoid, and 12 biphasic). Men accounted for 66% of the sample, and the median age was 64 years. Of the MM samples, 29 were from the MS801 tissue microarray and 50 MM were from the MS1001 tissue microarray (US Biomax, Rockville, MD); 16 MM were from the Unit of Pathology, IRCCS Azienda Ospedaliera Universitaria San Martino-IST-Istituto Nazionale per la Ricerca sul Cancro (Genoa, Italy); and 11 MM were from the Unit of Histopathology, ASL5 (La Spezia, Italy).

We found that none of the 106 MM samples (0%) showed *ROS1* or *ALK* gene rearrangement (Fig. 1).

We confirmed the percentages previously reported on the status *of MET* gene. Indeed, we found that two of 106 epithelioid MMs (1.9%) showed *MET* gene amplification (*MET*/chromosome enumeration probe 7 ratio = 4 and *MET*/chromosome enumeration probe 7 ratio = 6) and six of 106 MM samples (four epithelioid, one sarcomatoid, and one biphasic) (5.7%) showed high polysomy of *MET* in the range of six to10 spots of *MET* in about 60% to 80% of tumor cells.

Our letter is the first report that analyzes *ROS1* status by fluorescence in situ hybridization analysis in MM. We found that *ROS1* translocation is not present in MM and this gene does not seem to be a candidate target for crizotinib treatment in these patients.

However, *ROS1* translocation is also an infrequent event in NSCLC, in which it occurs in only 1% to 2% of tumors.[4] Therefore, we cannot exclude with absolute certainty that if we were to expand our series, *ROS1*

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