

Nucleus of the Tractus Solitarius Metastasis: Relationship to Respiratory Arrest?

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ABSTRACT: Background: A 52-year-old woman with metastases in brain and bone had clinical and radiological response to therapy but died about 10 weeks after diagnosis. General autopsy failed to identify a primary neoplasm or an anatomic cause of death. Investigation of sudden respiratory cessation was a consideration when undertaking an anatomic study of the brain. **Methods:** Review of patient records and careful examination of the brain following autopsy were carried out. **Results:** The patient had terminal episodes of hypersomnia but episodes of sleep apnea were not observed. She received no respiratory support and no respiratory difficulties were recorded until she was pronounced dead at 7 a.m. Autopsy revealed metastatic adenocarcinoma in a pattern suggestive of a primary pulmonary neoplasm, including multiple cerebral metastases, although no significant pulmonary lesions of any type were found. A 0.2 cm metastatic adenocarcinoma was found in the nucleus of the tractus solitarius (NTS). No other tumor was present in the brain stem. **Conclusions:** Unilateral destruction of the NTS in the medulla would have severely disturbed the most critical point of convergence of autonomic and voluntary respiratory control and of cardiocirculatory reflexes in the central autonomic network. It is postulated that this caused respiratory arrest during a state transition from sleeping to waking. Few metastases to the medulla are reported, most are relatively large, and several have caused respiratory symptoms before death. The very small metastasis in our patient could be the direct anatomic cause of death, and as such it is an unusual complication of metastatic disease of which clinicians should be aware. It is speculated that dysfunction of direct NTS connections to the pons or of connections passing close to the metastatic deposit resulted in terminal hypersomnia.

RÉSUMÉ: Métastases dans le noyau du faisceau solitaire: y a-t-il un lien avec l'arrêt respiratoire? Introduction: Une femme âgée de 52 ans porteuse de métastases cérébrales et osseuses a eu une réponse clinique et radiologique au traitement mais elle est décédée environ 10 semaines après le diagnostic. Une autopsie n'a pas pu identifier un cancer primaire ou une cause anatomique de décès. À l'examen anatomopathologique du cerveau, on a recherché la cause de l'arrêt respiratoire subit. **Méthodes:** Il s'agit d'une revue de dossiers de patients et d'examen anatomopathologiques de cerveaux. **Résultats:** La patiente a eu des épisodes d'hypersomnie en phase terminale mais aucun épisode d'apnée du sommeil n'a été observé. Elle n'a pas reçu d'assistance respiratoire et aucune difficulté respiratoire n'a été notée jusqu'à ce que son décès ne soit constaté à 7 am. Une autopsie a révélé un adénocarcinome métastatique dont l'aspect était suggestif d'une néoplasie pulmonaire primaire, dont de multiples métastases cérébrales, bien qu'on n'a retrouvé aucune lésion pulmonaire significative de quelque type que ce soit. Un adénocarcinome métastatique de 0.2 cm a été retrouvé dans le noyau du faisceau solitaire (NFS). Il n'y avait aucune autre tumeur dans le tronc cérébral. **Conclusions:** Une destruction unilatérale du NFS dans le bulbe aurait sévèrement perturbé le point de convergence le plus critique du contrôle respiratoire autonome et volontaire et des réflexes cardiocirculatoires dans le réseau autonome central. Nous postulons qu'il s'agit là de la cause de l'arrêt respiratoire pendant un état de transition entre le sommeil et l'éveil. Peu de métastases bulbaires ont été rapportées, la plupart étant relativement grosses et plusieurs ayant causé des symptômes avant le décès. La petite métastase chez notre patiente pourrait être la cause anatomique directe de son décès et comme tel il s'agit d'une complication inusitée de la maladie métastatique que les cliniciens devraient connaître. Nous émettons l'hypothèse qu'une dysfonction des connections directes entre le NFS et le pont ou des connections passant près du dépôt métastatique a causé l'hypersomnie terminale.

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Destruction of centres in the medulla in patients developing breathing irregularities or suffering respiratory arrest has been reported for tumors,¹⁻⁶ infarcts, infections, and other types of lesions.⁷⁻¹⁵ Key cardiorespiratory regions affected in the medulla most often include the nucleus of the tractus solitarius (NTS), the nucleus ambiguus, and the ventrolateral reticular formation.³⁻¹⁶ We report a patient with radiologically-demonstrated cerebral and osseous metastases who suffered a fatal respiratory arrest and who proved at autopsy to have only one small metastasis in the brain stem.

CASE REPORT

A 52-year-old previously healthy female smoker had sudden onset of seizures. Radiologic imaging revealed scattered cerebral and osseous lesions presumed to be metastatic carcinoma. No primary lesion was

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found. Seizures did not recur, but she developed confusion, headache, nausea and vomiting, and eventually weakness, dizziness, unsteady gait, regional extremity numbness, disorientation, memory loss and cognitive impairment. She also had sudden episodes of drowsiness during the day. She had no reported or witnessed respiratory difficulties. A course of whole-brain radiotherapy given in five fractions (2,000 cgy total) and dexamethasone was followed by symptomatic improvement and slight shrinkage of cerebral lesions. The only blood count abnormality was a slightly elevated red cell distribution width (17; high normal, 14.5). Serum CO₂ was in the reference range nine days before death. She was ambulatory until a week before she died. Following radiotherapy, only palliative care without respiratory support was provided. No further diagnostic measures were undertaken. Haloperidol was given until her final week. She was restless and agitated, and she continued to be drowsy, sleeping most of the time during the final week. She was maintained only under light sedation with 60 mg of phenobarbital every 12 hours (phenobarbital level was slightly below therapeutic range). Observations were done regularly every 15 minutes for nine days before death. No ataxic breathing was ever noted. Death was observed at 7 a.m. when the patient stopped breathing, about 10 weeks after the episode of seizures. There was no cardiac monitoring except in pronouncing death.

Careful search during the general autopsy revealed no anatomic cause of death. Microscopy revealed a 0.2 cm deposit of adenocarcinoma in a parabrachial lymph node and another in the right adrenal gland. There were small osseous metastases. Pneumonia was not found in the lungs and no pulmonary neoplasm was identified. External examination of the brain showed only slight gyral flattening. The circle of Willis and the vertebrobasilar arteries had mild arteriosclerosis. Coronal sections of the cerebral hemispheres revealed about a dozen widely scattered 0.2 cm to 1.5 cm lesions in the neocortex or at the corticomedullary border. The insula was not involved. The larger two lesions were gray-tan and partly cavitated. The smaller lesions were yellow-gray. Deep cerebral structures, cerebellum, brain stem, and upper cervical spinal cord were grossly normal. Microscopic sections of the cerebral lesions revealed adenocarcinoma with hemorrhage and cholesterol clefts. Some nuclear grooves and optically empty nuclei prompted an immunostain for thyroglobulin. This was negative, ruling out metastasis from the thyroid gland. Estrogen and progesterone receptor immunostaining that might be found in some breast and pelvic

tumors was also negative. These metastatic tumors resembled the osseous, adrenal and lymph node metastases. There was a 0.4 cm metastatic tumor in the inferior vermis of the cerebellum that had not been seen grossly. A 0.20 X 0.13 cm metastatic adenocarcinoma was in the right side of the dorsolateral medulla near the level of the pontomedullary junction, and it replaced the NTS at that level (Figure 1). A small rim of pallor adjacent to the metastatic tumor would have included subnuclei of the solitary tract and any other passing axons in this zone. Bielschowsky silver impregnation demonstrated the focal NTS destruction (Figure 1A). Multiple levels of the entire brain stem were examined and no other brain stem metastases were found. No leptomeningeal tumor deposits were found. A small metastatic tumor was present in the superficial aspect of a posterior horn of the upper cervical spinal cord.

DISCUSSION

Most metastases to the brain stem occur in association with cerebral metastases^{17,18} and they are usually due to pulmonary carcinoma,¹⁷⁻²⁴ as is metastatic disease to the brain in general.²⁵⁻²⁸ It has long been recognized that pulmonary carcinomas may have very small primary lesions, and in cases with cerebral metastases and no primary tumor identified at autopsy, the possibility of a pulmonary primary is often considered.^{17,29,30} Metastasis to the brain is common in lung cancer patients overall,^{31,32} and pulmonary adenocarcinoma is the single most common neoplasm to metastasize to the brain.^{25,27,33,34} Pulmonary adenocarcinomas also commonly metastasize to parabrachial lymph nodes, liver, adrenals, and bone.^{25,27} Except for a negative finding in the liver, this is the metastatic pattern in our case. Therefore, even without a primary tumor having been identified, the tumors in our case have every appearance of being metastatic from a lung. Pulmonary adenocarcinoma may present first as metastatic disease as in our patient, although this is uncommon.^{25,27,29,34}

Patients developing brain metastases from pulmonary adenocarcinoma have a shortened survival,³⁵ and this is true from intracranial spread of other malignancies.³⁶⁻³⁹ In general, the malignant process itself is considered as the cause of death

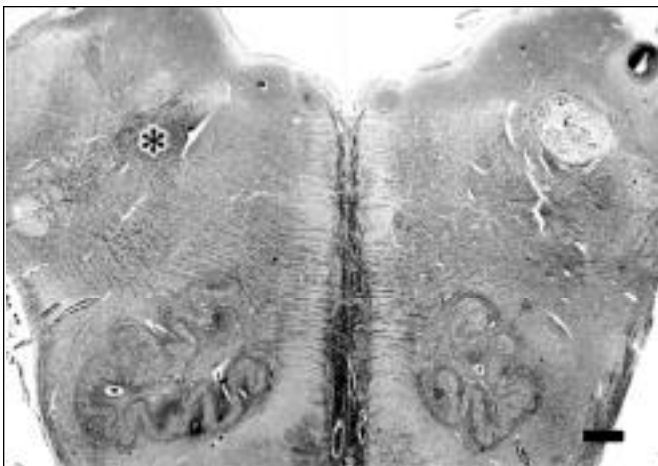


Figure 1A: Bielschowsky silver-impregnated composite view of upper medulla with normal nucleus of the tractus solitarius (*) on the left side and metastatic tumor replacing the nucleus on the right. Bar = 1 mm.

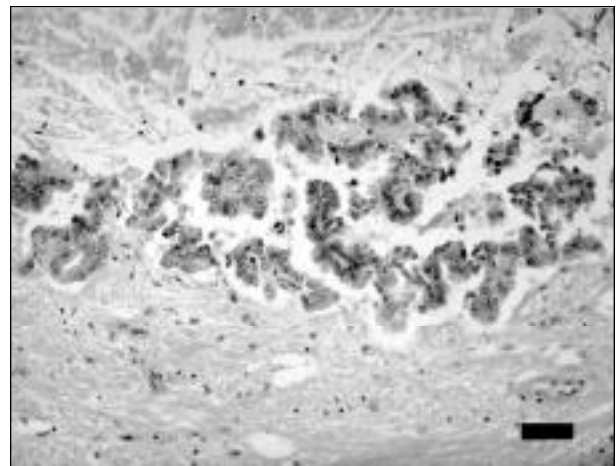


Figure 1B: H&E-stained section of region of nucleus of the tractus solitarius in right side of upper medulla showing metastatic papillary adenocarcinoma with viable tumor at brain margin and central necrosis. Bar = 200 µm.

when metastases are widespread to the brain and other organs, with the presence of coma, organ failure and metabolic abnormalities not recognized in our patient.⁴⁰ Cranial radiation can prolong survival in patients with brain metastases from pulmonary and other adenocarcinomas, and it is more likely to do so when brain is the only significant site of metastatic spread.^{31,39,41-44} The adverse effect of skeletal metastases appears to be significantly less than for brain metastases, even though pain, pathologic fractures and spinal cord compression can provide significant morbidity.^{37,45-51} For metastatic breast carcinoma, 9-14% of patients with brain metastases die from a central nervous system cause,^{45,52} and in similar studies of various primaries the majority of patients die of extracranial disease.^{28,53} For colorectal carcinoma, survival may not be affected by the presence or extent of metastatic brain disease.⁵⁴ The location of a single brain metastasis from non-small cell pulmonary carcinoma does not affect survival.⁵⁵ However, brain metastases are often multiple and non-small cell lung cancer deaths are more closely related to neurological causes in one study, although specific medullary involvement is not documented.⁵⁶ In our patient, the initial neurologic problems had not worsened after palliative treatment.

Metastatic tumors to the medulla oblongata are unusual, and most of them involve a relatively large proportion of medullary tissue at least on one side.^{2,6,17-19,21-23} Dorsolateral, dorsomedial and ventrolateral medullary regions are often destroyed in cases that provide detailed findings.^{2,5,6,18,19,21,22} Respiratory failure has only been reported in tumors metastatic to the medulla on a few occasions.^{1,2,6} A question arises concerning the role of a small, unilateral medullary lesion in causing respiratory arrest.

Unilateral destruction of the NTS appears to be one process in developing respiratory symptoms involving automatic responses, even though damage to other central autonomic centres may be required to cause autonomic respiratory failure.^{10,13} Some NTS axons may cross to the opposite side, which would explain a bilateral effect on respiratory drive from a unilateral lesion.¹⁰ Voluntary respiratory signals descend in the corticospinal tracts,⁵⁷ yet the NTS and other respiratory nuclei appear to have a role in the integration of automatic and voluntary respiratory efforts.¹⁰ The NTS is the nuclear and connecting structure that drives, monitors and modifies cardiac, circulatory and respiratory function. The NTS has critical connections to centres in the ventrolateral medulla driving cardiac signals and it is the central control point for cardiovascular and respiratory motor signals as they are passed on to other components of the central autonomic network. It receives input from cardiovascular receptors and it integrates autonomic afferent information with its own output and with integrated information from the rest of the central autonomic network to influence respiration and circulation.^{11,58,59} The interconnected dorsal and ventral medullary nuclear groups are primary sites that integrate and drive automatic respiration. The NTS itself is an important connection between dorsal and ventral areas that contribute bilateral inputs into the NTS, so that central medullary lesions will disrupt efferent second and afferent third order neurons transmitting signals of the respiratory central pattern generators.^{59,60} This prevents the final message to spinal motoneurons and prevents automatic initiation of respiratory muscle activity.^{61,62} Precise localization of respiratory drive and

relative functional strength at specific levels of connections varies between species⁵⁹ and these networks have yet to be adequately explored in man.¹⁴

A unilateral NTS lesion is not clearly demonstrated to have caused outright respiratory arrest, and respiratory failure is unusual even with documented medullary metastases. However, the lesion found in the central autonomic region in our patient is restricted to the NTS area. This includes a thin zone of immediately surrounding pallor that indicates edema which would be expected to be disruptive to passing axons of the reticular formation. Since the NTS is a major integration centre with known involvement in cases of respiratory difficulty,³⁻¹⁶ and since effects of the rim of apparent edema around the metastatic deposit would have only enhanced the dysfunction of adjacent central autonomic centres, the unilateral NTS-centred lesion is probably ultimately responsible for respiratory dysregulation leading to respiratory arrest.

Primary sleep apnea or sleep disordered breathing dissociated from waking respiratory problems is difficult to assign in this case, although it can occur with unilateral medullary lesions.^{10,13,14} Such an event would be described as Ondine's curse.⁶³ Our case may differ by demonstrating a dysregulation of the central autonomic network from the small, unilateral metastatic tumor in the critical NTS circulatory and respiratory initiation and relay centre, rather than by causing a block of descending respiratory drive. It is thought that in the immature nervous system the regulation of breathing is at risk during transition from sleep to the waking state.⁶⁴ Perhaps in this patient's mature nervous system, with focal destruction of the critical NTS region, a similar dysregulation occurred at this "state" transition. This may have led to sudden autonomic, as well as voluntary, dysfunction with failure of effective transition from one state to the other, resulting in respiratory or cardiorespiratory arrest. Given the scattered cerebral lesions, it is also possible that an effect on voluntary breathing may have occurred, and this might also be a factor in failed state transition. The possibility that a seizure was involved in respiratory arrest cannot be excluded,⁶⁵ although there was no documented seizure activity after the initial clinical episode. In fact, the cerebral metastases were reduced in size after radiotherapy and symptomatic improvement was noted.

There is no clinical or autopsy evidence of upper respiratory or peripheral pulmonary dysfunction in our patient, but hypersomnia was observed. Hypersomnia was not paired with apnea such as can occur in chronic pulmonary disease, and waking hypoventilation is not a feature in this case.⁶⁶ It is possible that the sudden episodes of drowsiness and terminal somnolence may have been contributed to by the solitary metastasis in the NTS zone since sedation remained at a low level terminally. The NTS has interconnections to pontine centres for the sleep-waking cycle⁶⁷⁻⁶⁹ and the rim of pallor around the metastatic deposit involves a central region of control in the brain stem reticular activating system.⁷⁰ However, another small brain stem lesion in the reticular activating system that could have been missed may have altered the sleep-waking cycle,⁷¹⁻⁷³ or a small unseen thalamic metastasis could have played a role in hypersomnia.⁷⁴

Sudden respiratory irregularities, and indeed sudden death, are potential problems faced by emergency medicine personnel

and by forensic specialists. Lesion of the central autonomic network by a variety of diseases is a well-known cause of respiratory abnormalities,¹¹ including rare cases of respiratory failure from a tumor metastatic to the medulla^{2,6} or encroaching on the medulla.¹ To this can be added metastatic carcinoma isolated to the NTS zone in the rostral medulla with a presentation of respiratory arrest as the only manifestation of respiratory failure. Terminal hypersomnia can be caused by a lesion of the brain stem central autonomic network, but whether it can be associated with a small disruption of the interrelated and neighboring NTS remains to be proved.

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