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Case 17-2015: A 44-Year-Old Woman with Intractable Pain Due to Metastatic Lung Cancer

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PRESENTATION OF CASE

Dr. Lecia V. Sequist: A 44-year-old woman with metastatic (stage IV) non–small-cell lung carcinoma was seen in the outpatient cancer center of this hospital because of intractable pain.

The patient had been well until approximately 1 year before this evaluation, when pain in her right shoulder and scapula developed, followed by cough and an episode of hemoptysis. A chest radiograph that was obtained at another hospital reportedly showed findings suggestive of pneumonia. Antibiotic agents were administered, but the pain and radiographic abnormalities persisted. Nine months before this evaluation, computed tomography (CT) of the chest revealed an irregular mass (3.5 cm by 3.7 cm by 5.0 cm) in the anterior right upper lobe, along with multiple pleural nodules (most <1 cm in diameter) in the right hemithorax and mediastinal and right hilar lymphadenopathy (with nodes ≤12 mm in diameter). ^{18}F-fluorodeoxyglucose positron-emission tomography and CT (PET–CT) reportedly revealed two indeterminate foci in the first and fifth lumbar vertebrae. Flexible bronchoscopy and mediastinoscopy with biopsy were performed.

Dr. Mari Mino-Kenudson: Examination of a pretracheal lymph node–biopsy specimen revealed that multiple lymph-node fragments had been almost completely replaced by metastatic tumor deposits (Fig. 1A through 1D). There was a solid growth of tumor cells with infrequent and incomplete gland formation, a finding consistent with poorly differentiated adenocarcinoma. Immunohistochemical staining for thyroid transcription factor 1 was positive in the tumor cells, a finding consistent with adenocarcinoma of the lung.

Because the patient had never smoked tobacco, genetic testing of tumor tissue for a mutation of the epidermal growth factor receptor gene (*EGFR*) was performed and revealed a deletion of 15 bp in exon 19 (Fig. 1E). A frameshift deletion mutation in exon 19 is known to confer sensitivity to EGFR tyrosine kinase inhibitors.

Dr. Sequist: Therapy with erlotinib hydrochloride (150 mg daily) was begun 7 months

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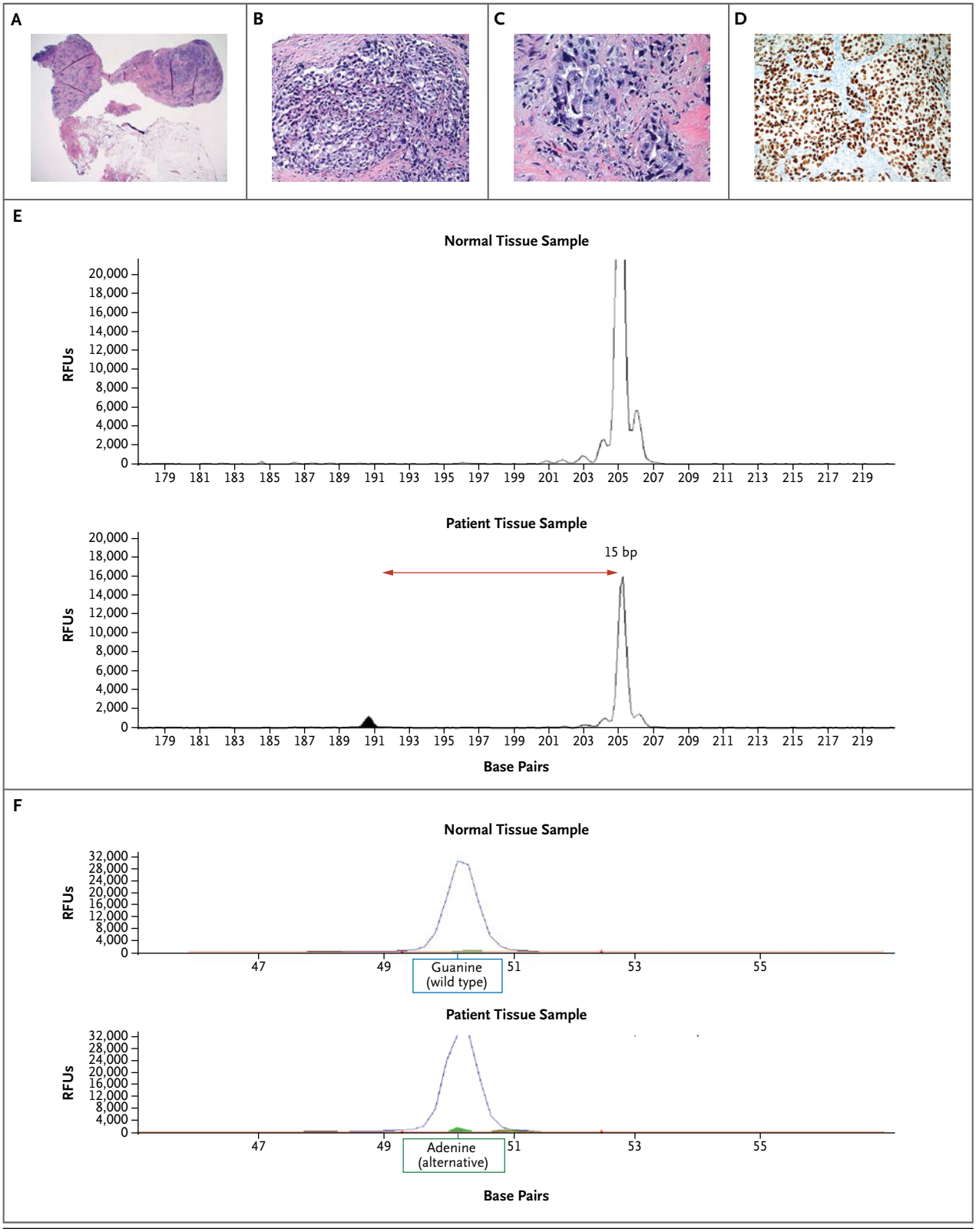

Figure 1 (facing page). Pathological Examination of Tumor Tissue.

Hematoxylin and eosin staining of a pretracheal lymph node–biopsy specimen shows that multiple lymph-node fragments are almost completely replaced by metastatic tumor deposits (Panel A). The tumor has a solid growth of atypical cells (Panel B). Infrequent and incomplete gland formation is also seen (Panel C), a finding consistent with poorly differentiated adenocarcinoma. Immunohistochemical staining for thyroid transcription factor 1 is positive in the tumor cells (Panel D), a finding consistent with adenocarcinoma of the lung. Results of genetic testing of the lymph node–biopsy specimen were obtained at the time of the diagnosis (Panel E). Total nucleic acid extracted from normal lung tissue (top) and that from the formalin-fixed, paraffin-embedded cell block of the patient's tissue sample (bottom) were run in parallel, and the results showed a deletion of 15 bp (between the arrows) in exon 19 of the epidermal growth factor receptor gene (*EGFR*) (black peak); this mutation is known to confer sensitivity to tyrosine kinase inhibitors. Results of genetic testing of cells in the pleural fluid were obtained at the time of recurrence (Panel F). Total nucleic acid extracted from normal lung tissue (top) and that from the formalin-fixed, paraffin-embedded cell block of the patient's tissue sample (bottom) were run in parallel. In addition to the original deletion mutation in exon 19, a point mutation that results in an amino acid substitution of a methionine for a threonine at position 790 in exon 20 was identified (green peak). This mutation (*EGFR* T790M) is known to confer resistance to tyrosine kinase inhibitors. RFU denotes relative fluorescence unit.

before this evaluation, and the patient's pain rapidly lessened. Three months after the initiation of erlotinib therapy and 4 months before this evaluation, CT of the chest reportedly revealed a decrease in the size and number of pulmonary nodules and up to eight new mixed lytic and sclerotic vertebral lesions. Erlotinib was continued, and zoledronic acid was begun. Two months before this evaluation, pain in the right shoulder worsened. Repeat CT, performed 18 days before this evaluation, reportedly revealed enlargement of the dominant mass in the right upper lobe and a new pleural effusion. The patient's oncologist recommended discontinuation of erlotinib and administration of standard chemotherapy for lung cancer.

Twelve days after erlotinib therapy was discontinued, the patient was seen in the outpatient cancer center of this hospital to discuss treatment options for erlotinib-resistant lung cancer. She reported incapacitating, stabbing pain that she rated as "up to 15" on a scale of 0 to 10 (with 10 indicating the most severe pain) and that had worsened since erlotinib therapy was discontinued. The pain extended from the right lower anterior thorax to the right shoulder and radiated through her chest to the entire right posterior chest wall; it worsened with breathing and lying down, and thus she was required to sleep in a recliner. When she took acetaminophen, hydrocodone, and ibuprofen regularly, the pain lessened to 6 out of 10. Other opioid analgesic agents had no effect or, more frequently, caused worsening pain.

The patient had undergone gynecologic and bladder surgery. She had no known allergies. She lived with her husband and teenaged children and had worked in an office. She drank alcohol infrequently and had never smoked or used illicit drugs. There was no family history of lung cancer.

On examination, the patient was tearful, huddled over, and holding a pillow to help ease her pain. The blood pressure was 142/80 mm Hg, the pulse 76 beats per minute, the temperature 36.2°C, and the respiratory rate 16 breaths per minute. There were decreased breath sounds and dullness on percussion at the right lung base and focal tenderness along the right thoracic paraspinal area and posterior chest wall (medial to the scapula); palpation did not reproduce the intense, gnawing pain deep in the right side of the chest that bothered her the most. The remainder of the examination was normal. The blood level of alanine aminotransferase was 59 U per liter (reference range, 7 to 30), and the level of aspartate aminotransferase was 33 U per liter (reference range, 9 to 32). The complete blood count was normal, as were levels of electrolytes, glucose, alkaline phosphatase, total bilirubin, total protein, albumin, globulin, and calcium and results of coagulation and renal-function tests. The next day, the palliative care service was consulted; however, despite adjustment of the patient's analgesic regimen, pain persisted.

Dr. Efren J. Flores: Two days after the patient's evaluation in the outpatient cancer center, CT of the chest, abdomen, and pelvis (Fig. 2A), performed after the administration of contrast material, revealed an irregular enhancing mass in

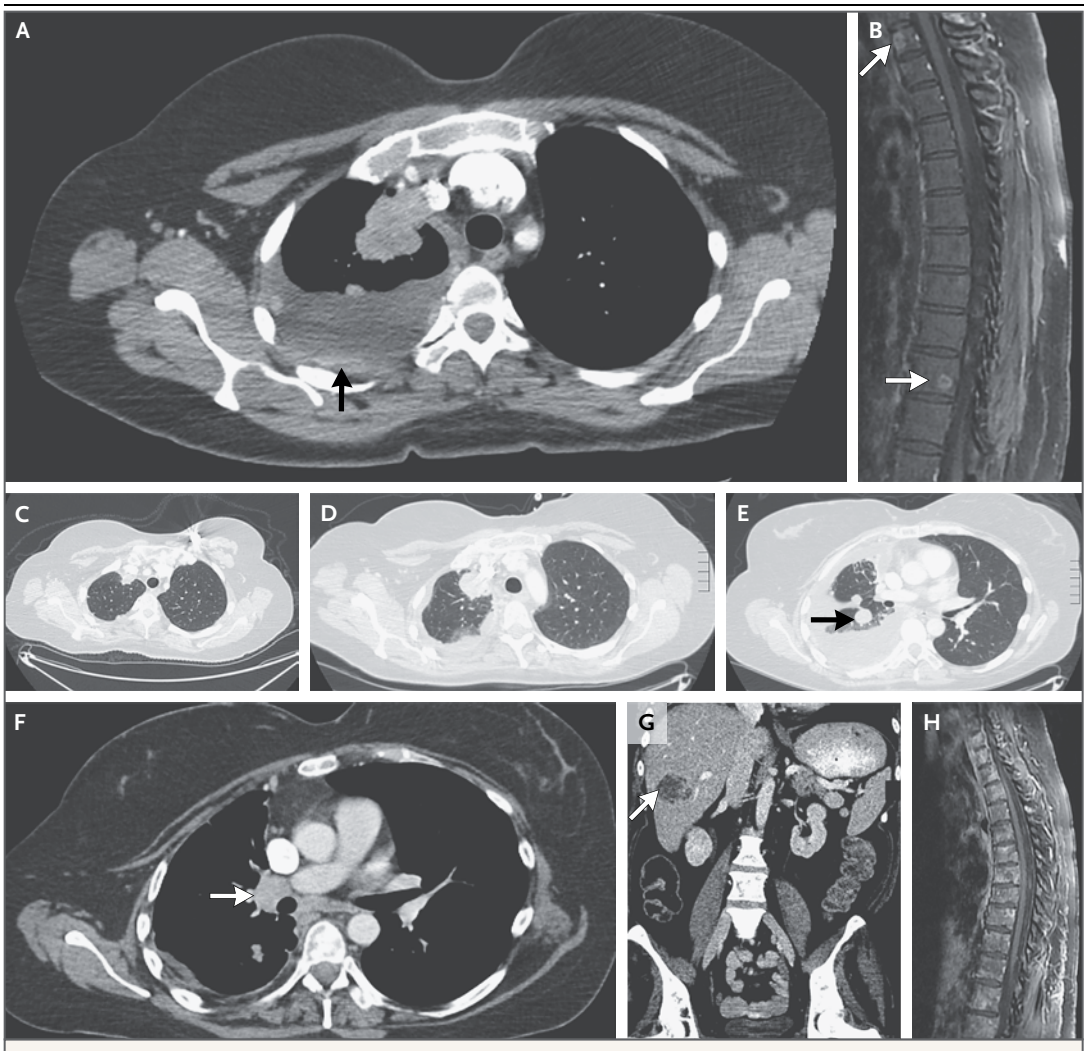

Figure 2. Imaging Studies.

Two days after the patient's presentation in the outpatient cancer center of this hospital, CT of the chest was performed after the administration of contrast material; an axial image (Panel A) shows a dominant mass in the right upper lobe (arrow), a large pleural effusion, and enhancing pleural nodules, findings consistent with pleural metastasis. Contrast-enhanced MRI of the thoracic spine was also performed at this time; a fat-saturated sagittal image (Panel B) shows enhancing lesions in the T1 and T10 vertebral bodies (arrows), findings consistent with osseous metastatic disease. Three months after the initial presentation, contrast-enhanced CT of the chest was performed; an axial image (Panel C) shows a decrease in the size of the mass in the right upper lobe and the pleural effusion and a decrease in the number of pleural nodules, findings consistent with reduced pleural metastasis. Twelve months after the initial presentation, contrast-enhanced CT of the chest was performed; axial images (Panels D and E) show enlargement of the dominant mass in the right upper lobe and right pleural effusion and new lung nodules (Panel E, arrow), findings consistent with disease progression. Eighteen months after the initial presentation, contrast-enhanced CT of the chest and abdomen was performed; an axial image (Panel F) shows new mediastinal lymphadenopathy (arrow), and a coronal image (Panel G) shows a new heterogeneously enhancing liver metastasis (arrow). Contrast-enhanced MRI of the thoracic spine was also performed; a fat-saturated sagittal image (Panel H) shows multiple enhancing lesions throughout the thoracic spine, a finding consistent with progression of diffuse osseous metastatic disease.

the right upper lobe and a large right pleural effusion with pleural nodules. Magnetic resonance imaging (MRI) of the thoracic spine (Fig. 2B), performed after the administration of contrast material, revealed multiple enhancing lesions (≤1.1 cm in diameter) in the thoracic vertebrae, a finding consistent with osseous metastatic disease.

Dr. Sequist: The patient remained in severe discomfort and was admitted to this hospital 8 days after her initial evaluation at the cancer center. Erlotinib therapy was resumed at a dose of 150 mg daily.

Management decisions were made.

DISCUSSION OF MANAGEMENT

DISEASE FLARE AFTER DISCONTINUATION OF AN EGFR INHIBITOR

Dr. Sequist: The patient was initially treated with erlotinib. Multiple randomized, controlled trials have shown that, for patients with *EGFR* mutations, first-line EGFR inhibition yields better responses, longer disease control, and better quality of life than does first-line chemotherapy.[1-3] EGFR inhibitors typically control the disease for 1 to 2 years before resistance develops. However, even when radiographic progression is noted, a large portion of the overall tumor burden may remain effectively suppressed by the EGFR inhibitor. Stopping the drug can cause the rest of the disease to flare, leading to hospitalization or even death in up to 25% of cases.[4] This patient had a characteristic disease flare after discontinuation of erlotinib, resulting in admission to the hospital for a pain crisis. It is now recommended to consider continuing EGFR inhibitors even after disease progression to avoid such flares as the one seen in this case.

In anticipation of the patient's enrollment in a clinical trial, thoracentesis of the pleural effusion was performed during the first admission to this hospital, both to relieve dyspnea and to obtain tumor cells for further genetic testing. Unfortunately, only a small amount of fluid could be removed and the procedure caused worsening pain, requiring admission to the hospital later that day.

Dr. Mino-Kenudson: The pleural fluid contained cells that were consistent with the patient's known adenocarcinoma. Sequencing of *EGFR* revealed, in addition to the deletion mutation in exon 19,

Table 1. Analgesic Agents Administered in This Patient and Remaining Therapeutic Options for Refractory Cancer-Related Pain.

Analgesic agents administered in this patient
Systemic opioids
Morphine and extended-release morphine
Oxycodone and extended-release oxycodone
Intravenous and oral hydromorphone
Methadone
Intravenous and transdermal fentanyl
Oxymorphone
Tramadol
Tapentadol
Hydrocodone with acetaminophen
Intrathecal agents
Morphine
Hydromorphone
Bupivacaine
Clonidine
Nonopioids
Acetaminophen
Nonsteroidal antiinflammatory drugs (ibuprofen, nabumetone, topical diclofenac, and intravenous and oral ketorolac)
Nortriptyline
Gabapentin
Pregabalin
Duloxetine
Dexamethasone
Tizanidine
Lidocaine (5% patch)
Intravenous ketamine
Bisphosphonates
Remaining therapeutic options
Intrathecal ziconotide
Intrapleural analgesia
Buprenorphine
Cannabinoid therapy
Intravenous lidocaine
Radionuclides
Percutaneous cryoablation
Palliative cordotomy
Radiation therapy
Palliative sedation

a point mutation that resulted in an amino acid substitution of a methionine for a threonine at position 790 in exon 20 (Fig. 1F). This mutation (*EGFR* T790M) is known to confer resistance to tyrosine kinase inhibitors.

MANAGEMENT OF REFRACTORY CANCER-RELATED PAIN

Dr. Mihir M. Kamdar: My colleagues in the palliative care and pain medicine services who cared for the patient were faced with a dilemma. The functional status of this young woman with a terminal diagnosis was so compromised by unrelenting pain that she could not begin her next chemotherapeutic regimen, and her pain was either not helped or seemingly made worse by most analgesics.

The World Health Organization (WHO) "ladder" for cancer-related pain is a well-validated and generally effective approach to pain management that recommends nonopioid therapy for mild pain and opioid therapy for moderate or severe pain.[5,6] However, 12 to 14% of patients have poorly controlled pain despite adherence to WHO guidelines.[5,6]

For patients with cancer-related pain that is refractory to opioids, treatment options include opioid rotation, optimization of nonopioid analgesics, and interventional therapies.[7,8] This patient had tried numerous opioids (Table 1), and aside from hydrocodone, these agents were ineffective and paradoxically frequently worsened her pain. Ketorolac was the only effective nonopioid analgesic.

Therapies that target the underlying source of cancer-related pain should always be considered. A consultant from the radiation oncology service found that the location and nature of the patient's pain did not correlate with an anatomical lesion for which radiation would have been an effective treatment. Thoracentesis of the pleural effusion had resulted in worsening pain.

For cancer-related pain that is unresponsive to systemic analgesics, a fourth step on the WHO ladder — interventional therapies — has been proposed.[9,10] Data suggest that interventions such as neurolytic blocks and neuraxial drug delivery may yield improved pain control with fewer side effects, as compared with systemic opioid therapy.[11,12] We recommend that interventional therapies be considered earlier and in tandem with therapies on the WHO ladder rather than held in reserve for the treatment of refractory pain.

Because this patient's pain was not responding to systemic opioids, a trial of intrathecal drug delivery was recommended. Intrathecal drug delivery involves infusion of opioids and other analgesics into the subarachnoid (intrathecal) space in direct proximity to opioid receptors in the dorsal horn of the spinal cord, where small doses can have profound analgesic effects and cause fewer side effects than would systemic opioids.[12-14] During the patient's first admission to this hospital, a trial of intrathecal drug delivery with a temporary percutaneous catheter provided effective analgesia; a permanent intrathecal drug-delivery system was subsequently surgically implanted, and the patient was discharged. After several weeks, however, her pain began to escalate and she was readmitted to this hospital. She was treated with carboplatin, pemetrexed, and erlotinib, and her intrathecal pump was adjusted. After a few days, her pain lessened and she was discharged.

After discharge, the patient's pain was controlled for several months and she was able to spend quality time with her family and church community. Pain in the right thigh due to a metastasis to the femur was treated with radiation at another institution. The radiation therapy was associated with worsening fatigue and did not reduce her pain. Adjustment of the intrathecal analgesic regimen reduced the pain. Eventually, chemotherapy-related fatigue worsened, and her regimen was narrowed to erlotinib.

Dr. Flores: Three months after the initial presentation to this hospital, CT of the chest (Fig. 2C), performed after the administration of contrast material, revealed a decrease in the size of the mass in the right upper lobe and the pleural effusion and a decrease in the number of pleural nodules, findings consistent with reduced pleural metastasis.

Twelve months after the initial presentation to this hospital, pain in the right side of the chest and shoulder recurred. Axial images, obtained from a contrast-enhanced CT scan of the chest, showed enlargement of the dominant mass in the right upper lobe and right pleural effusion (Fig. 2D) and new lung nodules (Fig. 2E), findings consistent with disease progression.

Eighteen months after the initial presentation to this hospital, CT of the chest, abdomen, and pelvis, performed after the administration of contrast material, revealed continued enlargement of the mass in the right upper lobe (not shown), with new lung nodules and new mediastinal lymphadenopathy (Fig. 2F). A coronal image of the abdomen (Fig. 2G) showed a new heterogeneously enhancing liver metastasis. MRI of the thoracic spine (Fig. 2H) revealed multiple enhancing lesions throughout the thoracic spine, findings consistent with progression of osseous metastatic disease.

Dr. Kamdar: Pemetrexed therapy was restarted; however, the analgesic benefit was more moderate than it had been before and the therapy was associated with severe fatigue. Several interdisciplinary discussions of the goals of care were held, and the patient declined further chemotherapy or consideration of clinical trials. Her goal was to spend time at home with her family, and she was enrolled in home hospice care.

The patient was readmitted to this hospital briefly for worsening pain in the right side of the chest and midback. Radiation was recommended, but the patient declined because of previous side effects, lack of benefit, and her desire to maximize time at home. The analgesic regimen was adjusted, and she was discharged home, but after a few weeks, she again required admission for a pain crisis.

On admission, the patient reported severe neck pain, back pain, headache, difficulty keeping her head upright, numbness on the right side of the face, and weakness of the arms and legs and was bedbound. Adjustment of the intrathecal analgesic regimen now seemed to cause paradoxical worsening of pain. The clinical team was concerned about the patient in terms of brain metastases, multilevel compression of the spinal cord, and her entering the dying process.

I would like to reflect on two key questions in this case. First, why was her pain so refractory to usual measures? Second, why did opioid therapy worsen her pain?

In patients with refractory cancer-related pain, it is important to screen for nonphysiological factors that may contribute to the experience of pain, including existential suffering, spiritual distress, addiction, and psychological secondary gain.[15] Over the course of nearly 2 years, palliative care and oncology teams had worked together to engage the patient in open dialogue about her prognosis and to prepare her for dying. There was consensus among her team that neither existential suffering nor spiritual distress was driving her pain. Furthermore, the intensity of her pain correlated with changes in her tumor burden, which argues against any nonphysiological contribution to her pain.

When considering physiological causes of this patient's refractory and paradoxical pain, opioid-induced hyperalgesia should be high in the differential diagnosis. Opioid-induced hyperalgesia is a phenomenon whereby exposure to opioids sensitizes a patient to a pain stimulus, causing a paradoxical increase in pain, as seen in this patient.[16] The risk factor is chronic exposure to high-dose systemic opioids, which was present in this case, but there have been reports of opioid-induced hyperalgesia in patients who have not previously received opioids, patients receiving low-dose opioids, and patients receiving intrathecal analgesia.[16-19] Central activation of the *N*-methyl-D-aspartate (NMDA) receptor has been suggested as one possible cause,[16,17,20] and administration of NMDA antagonists has been recommended when opioid-induced hyperalgesia is suspected. However, the administration of NMDA antagonists (ketamine and methadone) yielded no benefit in this patient.

Opioid-induced hyperalgesia is a clinical diagnosis, so it is impossible to determine its role in this case with certainty. However, the patient's paradoxical increase in pain with opioid exposure raises suspicion for this phenomenon.

We tried numerous analgesic options for the patient during the course of her illness (Table 1). Unfortunately, the remaining options were either unlikely to yield a substantial benefit or were unacceptable to the patient. We worried that a time might come when we could no longer control her pain, and before the most recent admission, the interdisciplinary team had begun discussions about palliative sedation as a means to alleviate intractable pain at the end of life.

PALLIATIVE SEDATION FOR INTRACTABLE PAIN IN TERMINALLY ILL PATIENTS

Dr. Kathleen P. Doyle: Over the course of many admissions, we had discussions with the patient about her values and goals. She was deeply reli-

Table 2. Features of Sedation Interventions.

Intervention	Cause of Death	Intention of Intervention	Legal Status
Respite sedation	Underlying disease	Alleviation of acute symptoms after a predetermined interval of use	Legal in the United States
Palliative sedation	Underlying disease	Relief of intolerable symptoms	Legal in the United States
Physician-assisted suicide	Medication(s) prescribed by a physician and used by the patient	Termination of life	Legal in Montana, Oregon, Vermont, and Washington
Euthanasia	Medication(s) administered by a physician	Termination of life	Illegal in the United States

gious and a dedicated mother. She did not believe that God wanted her to suffer, and she had a sense that there was some greater purpose to her illness. She had hoped to die at home but recognized that it would be too difficult for her family. Her two greatest fears were that she would die in horrible pain and that her children would lose their faith because of her illness and suffering. In the preceding months, she had gently prepared her family for her eventual death. She felt desperate both for more time to care for her family and for pain relief.

Palliative sedation is an intervention to relieve intractable pain in terminally ill patients by means of continuous infusion of a sedation medication.[21-23] The discomfort of most dying patients can be controlled with state-of-the-art palliative care, but occasionally, there are patients whose symptoms cannot be controlled. In these rare cases, we consider palliative sedation. When this topic had been discussed previously, this patient was comforted that something could be done if the pain became unbearable.

On the most recent admission, the patient's pain was no longer responsive to ketorolac, glucocorticoids, hydrocodone, and intrathecal analgesic agents; the pain prevented her from sleeping, eating, drinking, and even lying still. Relief occurred only when she took lorazepam, which induced deep sleep. However, when the effect wore off, she awoke in agony. She requested that we initiate palliative sedation. Since she had previously expressed understanding and acceptance of this option, we did not think that this decision was made in an isolated moment of distress. The patient could articulate the potential ramifications of palliative sedation and declined artificial nutrition and hydration. Before proceeding, she asked that we meet with her family without her so their concerns could be voiced openly.

Members of the palliative care team (including me, Mr. Rinehart, and Dr. Kamdar), ethics team, and nursing team met with the patient's husband, children, siblings, parents, and pastor. We explained palliative sedation and its likely outcome and invited questions. One question was whether we could sedate her for a period and then stop. We had considered this, but we had no reasonable options to treat the pain that we expected would recur when she awoke. Once they came to the conclusion that the patient had endured immense suffering, they decided that everything should be done to help her be comfortable.

The staff subsequently met alone. The palliative care team discussed how difficult it is to treat a patient in this condition. We emphasized that anyone who felt uncomfortable providing palliative sedation could verbalize their concerns and excuse themselves from participating in the process. Having witnessed the patient's suffering, every team member was at peace with the decision to participate. Our goal was to use the lowest possible dose of medication required for pain relief, monitor for effect, and adjust the dose only if necessary to achieve comfort. The patient was initially given two boluses of lorazepam, and a low-dose lorazepam infusion was initiated. An intrathecal analgesic regimen was continued at a level that would provide as much analgesia as possible without causing hyperalgesia or increased

Table 3. Principle of Double Effect.

The action must be either morally good or neutral.
The bad effect must not be the means by which the good effect is achieved.
The only intention must be achievement of the good effect, and the bad effect must be only an unintended side effect.
The good effect must be at least equivalent in importance to the bad effect.

intraspinal pressure. For the first 24 hours, the patient was sedated and did not report any pain; however, after 24 hours she awoke in severe pain. She told us that she had no pain while she was sleeping. Despite the administration of additional boluses of lorazepam and an increase in the hourly infusion rate, pain continued. A propofol infusion was begun at the lowest dose, in accordance with this hospital's palliative sedation policy, and the dose was increased in a stepwise manner during the next 36 hours in response to persistent pain. The patient was monitored closely; medications were adjusted only to treat observed evidence of discomfort and were adjusted to the lowest possible dose necessary to achieve comfort, in an effort to minimize respiratory depression. For the next 48 hours, the patient was able to rest comfortably while receiving stable doses of a combination of lorazepam and propofol. She died with no evidence of discomfort, with her family at her side, 4 days after the initiation of palliative sedation.

Psychosocial Considerations

Mr. Todd J. Rinehart: Palliative sedation is emotionally and ethically challenging for all involved. This patient's ability to gracefully deal with the severity of her illness and simultaneously prepare her family for her death was profound. She spoke openly about her end-of-life wishes, always emphasizing not wanting to die in severe pain.

The decision to pursue palliative sedation in this case was the culmination of many multidisciplinary conversations with the patient and her family. After making the difficult decision to pursue palliative sedation, the patient expressed great sadness but also a sense of relief that her suffering could be alleviated.

As a social worker, my role is to attend not only to the needs of the patient and family but also to the needs of the members of the care team. Because of the emotional intensity and ethical complexity involved, the decision to offer palliative sedation is never easy. Therefore, regular debriefing sessions were held to allow team members at all levels to reflect on the experience. During these sessions, no one expressed regrets, although some spoke of the emotional and ethical processing they went through to better understand a procedure that was unfamiliar to them.

Ethical Considerations

Dr. Guy Maytal: How can we be sure that palliative sedation was an ethical intervention in this case? Palliative sedation is distinct from other sedation interventions performed at the end of life, such as respite sedation, physician-assisted suicide, and euthanasia (Table 2). In respite sedation, the patient is sedated for a predetermined period, after which sedation is lifted to assess the response. Patients are sometimes able to tolerate their symptoms better after respite sedation is discontinued; this would not have been the case for this patient.[24] Respite sedation and palliative sedation are both ethically distinct from physician-assisted suicide and voluntary active euthanasia, neither of which was considered in this case.[25,26] In palliative sedation and respite sedation, the intention is to alleviate pain and suffering but not to hasten death. The intention in physician-assisted suicide and voluntary active euthanasia is also to relieve unacceptable suffering, but the intervention intentionally ends the patient's life.[27]

There is a robust legal foundation for the initiation of palliative sedation as it was used in this case. When the U.S. Supreme Court ruled that physician-assisted suicide is not a constitutional right, it affirmed that patients with terminal illness who are experiencing great pain should have "no legal barriers to obtaining medication, from qualified physicians, to alleviate that suffering, even to the point of causing unconsciousness and hastening death."[28,29] Both the American Medical Association and the National Ethics Committee of the Veterans Health Administration have issued ethics policies endorsing the use of palliative sedation in cases such as this one.[30,31]

What is the ethical justification for the clinical use of palliative sedation in this case? The relevant ethical principles include autonomy, beneficence, nonmaleficence, and proportionality. Autonomy (the principle that individual freedom to make choices is safeguarded) is upheld in this case because the decision to initiate palliative sedation was made with the patient's full consent.

The remaining three principles are embodied in the principle of double effect (Table 3), which states that as long as the only intention of an intervention is to achieve a morally good outcome (e.g., alleviating intractable pain and suffering) through a morally good or neutral action (e.g., administering sedation medications), then even if there are unintended bad effects (e.g., the patient does not wake up from sedation and her life is shortened by a small amount), the intervention may proceed. The bad effects can be foreseen but cannot be intended. The principle of double effect provides clinicians with an ethical framework in which to think through the acceptability of interventions in a case such as this one.

Principle-based ethics are an important part of ethical reasoning, but in the end, principles do not make decisions; people do. When applying ethical principles, the clinicians in this case took into account the human context and the narrative (i.e., the history of interactions, decisions, and interpretations among the patient, her family, and the medical team) regarding this clinical situation. This patient's suffering had become intolerable. The medical team had exhausted all reasonable interventions. Her pain prevented her from engaging in even the most basic of human functions. Her decision to pursue palliative sedation came after a long process of conversations with her medical team and family, all of whom agreed to this course of action. She consented to the procedure and articulated that it was consistent with her values and her life narrative. In this case, palliative sedation was clearly an ethical intervention.

Dr. Nancy Lee Harris (Pathology): Are there any questions or comments?

Dr. David P. Ryan (Oncology): How often do we use palliative sedation at this hospital?

Dr. Vicki Jackson (Palliative Care): I would like to emphasize that this is a rare procedure that we use once or twice a year.

ANATOMICAL DIAGNOSIS

Adenocarcinoma of the lung with *EGFR* mutations, metastasis to the chest wall and bone, and intractable pain.

This case was discussed at the Cancer Center Grand Rounds.

Dr. Kamdar reports receiving fees from Amorsa Therapeutics for serving on an advisory board. Dr. Sequist reports serving as an unpaid consultant for Boehringer Ingelheim, Clovis, Merrimack Pharmaceuticals, AstraZeneca, Taiho, Genentech, and Novartis. Dr. Mino-Kenudson reports receiving consulting fees from Merrimack Pharmaceuticals. No other potential conflict of interest relevant to this article was reported.

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