Systemic fungal infection following effective pain relief with high-dose steroid therapy for terminal cancer pain
—A case report—

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High-dose steroid therapy is known as effective adjuvant therapy for refractory bone pain due to metastasis of solid cancer. However, the standard dose and duration have not been established to date. Long term maintenance with steroid therapy is not encouraged due to its potential adverse effects. Here, we report a case of a terminal cancer patient who maintained high-dose steroid therapy to alleviate refractory bone pain with complication of systemic fungal infection. (Anesth Pain Med 2015; 10: 61-63)

Key Words: Candida, Pain, Steroids.

A 53-year-old man referred to our pain clinic from oncology department for severe right shoulder pain over a period of two months. Three years earlier, this patient had been diagnosed with tongue cancer with locally advanced state (T3, N2, M0). Because the patient was initially in inoperable condition, the attending physician decided to treat him with the concurrent chemo-radiation therapy. His disease status was stable for three years. Three months earlier, he felt a progressive pain in his right shoulder. On his first visiting day, pain was continuous, ranging from 9 to 10 on the Visual Analog Scale (VAS). The pain was most severe in the right shoulder and proximal upper arm which radiated to the most distal part of the arm. He had also complained of paresthesia, numbness, and mild motor weakness of the right arm. Although the motor power of right arm was determined as grade 4, it affected his daily living activities. Imaging studies revealed bone metastasis with bone destruction of the right shoulder, ribs, and multiple spine metastasis (Fig. 1). His brachial plexus was metastasized. The attending physician deferred further chemo- or radiation therapy due to his poor general condition. The physician tried to control the pain with oral and patch analgesics. However, along with the progression of the pain, the dose of analgesics were increased up to a dose of 50 μg/hr of fentanyl patch, 80 mg/day of sustained-release oxycodone hydrochloride, 450 mg/day of pregabalin, and multiple doses of rapid-release oxycodone hydrochloride for the breakthrough pain. Together
with the oral medications, we tried peripheral nerve block several times, including his right 4/5th intercostal nerve block and supra-scapular nerve block. However, the patient still felt severe pain at VAS score of 9/10. Therefore, we decided to control the patient with high dose systemic steroid because the patient could not tolerate the side effects from oral analgesics such as anorexia, continuous nausea refractory to the prokinetics, and severe lethargy. Peripheral nerve blockades were not effective. In addition, brachial plexus block or cervical epidural block was not feasible due to limited access route caused by inflammatory edema, soft tissue deformities, tumor metastasis, and poor general condition. Neurodestructive interventions were not considered as feasible because they would further worsen his motor weakness which could lead to deterioration of his already poor general condition. Therefore, we started high-dose prednisolone therapy with initial dose of 60 mg/day for 10 days. We maintained the same dose for another 10 days. After that, his VAS score was declined to 2/10. With a good result, we tapered the dose to 40 mg/day for 3 days, and then 20 mg/day thereafter. But, on the day 15 of steroid therapy, he came to the emergency room with fever and chilling sensation. His vital signs were stable (blood pressure 120/80 mmHg, heart rate 72 /min, respiratory rate 20 /min and body temperature 37.1°C). No inflammatory focus was found by physical examination. His chest roentgenography showed the infiltration in the left lower lung field. A complete blood cell count at admission revealed upper-normal range of leukocytosis (9,900 mm³, 82% neutrophils) and elevated C-reactive protein concentration (6.98 mg/dl). The patient was admitted to the hospital via emergency room. Computed tomography of the lung showed patchy and nodular infiltration in the left lower lobe. He was treated with empirical antibiotics. Steroid therapy was withdrawn immediately. On hospital day 3, Candida albicans was grown in three cultures of blood drawn at the time of admission to the hospital. We treated him with the combination of usual antibiotics and anti-fungal agent. The infectious condition was not controlled despite of intensive medical treatment. He was expired on hospital day 63.

**DISCUSSION**

Severe cancer pain including metastatic bone pain is one of the major determinants of quality of life and even survival in terminally ill cancer patients. Several modalities have been tried to control this major problem of cancer patients. In general practice guideline, high dose morphine titration is usually accepted as treatment of choice. Non-steroidal anti-inflammatory drugs and other opioids, antidepressants, and anticonvulsants are considered as effective adjunctive treatment [5]. However, the standardized treatment or guideline for refractory cases with standard pain control modalities is not established to date [4]. High-dose steroid therapy was reported as effective therapeutic modality in these refractory cases [2,6,8]. In our case, the addition of high dose steroid was very effective, manifested as reduction of VAS score from 10 to 2. The patients was also satisfactory at the treatment.

Detailed mechanism of steroid on cancer pain was not so well elucidated. Reduction of peri-osteal edema and stretching has been suggested in some studies [6]. The optimal dose of steroid was not so well established. Some experts recommended the usage of high doses for cases of cancer pain [3]. Despite of its effectiveness on the pain control, subjective well-being, and other nonspecific symptoms of advanced...
cancer, there are many adverse effects related to the steroid such as opportunistic infection, tissue edema, dyspepsia, psychiatric changes including insomnia and muscle weakness after proximal myopathy, which are important information for the pain clinicians [6]. The opportunistic infection is the most lethal complication of high-dose steroid therapy, as shown in our case. It is well known that the high dose steroid is related to the T-cell dysfunction and deterioration of cell mediated immunity. The decision of long-term high dose steroid therapy was inevitable in our case due to many factors, including 1) increasing the dose of opioids and anti-convulsants were not feasible due to its side effects; 2) some peripheral nerve blockades were not effective; 3) brachial plexus block or cervical epidural block was not feasible due to limited access route (caused by inflammatory edema, soft tissue deformities and tumor metastasis) and poor general condition; 4) neurodestructive intervention was not feasible due to progressive motor weakness. The combination of these factors influenced our decision to treat the patient with high dose steroid because we thought further interventions might have low benefit/risk ratio. However, as a result, the accumulated dose was up to 760 mg, which lead to systemic fungal infection. The systemic fungal infection in our case might not be solely caused by the high dose steroid alone, but it was largely caused by this therapy as steroid therapy was well-established risk factor of candida infection [9]. Although high dose steroid therapy would be a ‘last resort’ for the intractable cancer pain, there were no established guidelines regarding its dose and schedule. The dose of steroid we used in the current case was somewhat empirical, as the dose was tapered as soon as the pain reduction effects were manifested. Some experts proposed that the high dose dexamethasone (up to 80 mg/day) could be utilized in the terminally ill patients, to 80 mg/day) could be utilized in the terminally ill patients, Some experts proposed that the high dose dexamethasone (up to 80 mg/day) could be utilized in the terminally ill patients, [4]. The seminar work from Weissman et al. [10] reported toxicity of steroid depended on the total dosage (> 400 mg of prednisolone) and duration (>3 weeks of therapy). Therefore, the use of “least effective dose” of steroid “as short as possible” would be the most effective and safe strategy in these patients. Intensive monitoring for efficacy, tolerance and adverse effect should be warranted [3]. If significant adverse effects occurred during the course of the therapy, it should be withdrawn immediately so that the total duration of the therapy would not exceed 3 weeks [11]. Otherwise, it should be tapered slowly to avoid risk of adrenal insufficiency. Although some authors claim that continuous use of high-dose steroid could be justified in patient with a limited life expectancy [4], aggressive nerve blockades and neurolytic blocks should be considered to diminish the total analgesic doses (including steroid), therefore helping the patients in terms of pain improvement and less-side effects [12].

In conclusion, high-dose steroid therapy is an effective adjuvant therapy on refractory cancer pain. However, it could be associated with severe adverse effects. The shortest duration of bridging steroid therapy with the definite treatment or neurodestructive intervention should be effective and safe strategy for these patients.

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