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Case Report

Combined Chemotherapy with Carboplatin Plus Irinotecan Showed Favorable Efficacy in a Case with Relapsed Small Cell Carcinoma of the Prostate Complicated with Meningeal Carcinomatosis

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Abstract

We report the case of a 65-year-old man with recurrent prostate cancer presented with meningeal carcinomatosis.

In September 2007, he was diagnosed with mixed type small cell carcinoma and adenocarcinoma at clinical stage T4N1M1 (primary prostate tumor with multiple bone, liver, and lymph node metastases) and hormonal therapy was administered. Following increase in level of pro-gastrin-releasing peptide (ProGRP) combined chemotherapy with cisplatin plus etoposide was implemented and showed efficacy in targeting small cell carcinoma. In March 2008, presenting with signs of meningeal irritation, his condition deteriorated quickly and multiple brain metastases were confirmed by magnetic resonance imaging (MRI). A sample of cerebrospinal fluid collected by lumbar puncture showed cancer cells and elevated level of ProGRP. Small cell carcinoma of the prostate complicated with meningeal carcinomatosis was diagnosed. A different regimen was then administered consisting of combined chemotherapy of carboplatin plus irinotecan, which is one of the most common 1st line treatments for extensive stage small cell lung carcinoma. From day 20 after initiation of this therapy, he gradually recovered from signs of meningeal irritation, as brain MRI

showed nearly normal findings, and serum level of ProGRP was improved.

We report the efficacy of combined treatment with carboplatin plus irinotecan for small cell carcinoma of the prostate complicated with meningeal carcinomatosis. Because this clinical condition is extremely rare, a gold standard treatment has yet to be established.

Key words

Prostate, small cell carcinoma, chemotherapy, meningeal carcinomatosis, ProGRP, refractory case

Introduction

Small cell carcinoma of the prostate (SCCP) is rare accounting for just 0.5% to 2% of all prostatic malignant tumors [1].

In general, clinical features of SCCP include visceral metastases, high incidence of osteolytic bone lesions, unresponsiveness to hormone therapy, decreased level of serum prostate-specific antigen (PSA), and a high response rate to cisplatin plus etoposide chemotherapy [2, 3].

The prognosis of SCCP is poor with a median survival range of 5 to 17.5 months [1] and the optimal treatment especially in relapsed chemotherapy treated patients, is not clearly established.

We report a case of refractory relapsed small cell carcinoma of the prostate, complicated with meningeal carcinomatosis, in which combined chemotherapy with carboplatin plus irinotecan was effective.

Case report

We report the case of a 65-year-old Japanese man with a history of recurrent prostate cancer presented with carcinomatosis.

At the age of 64 years, he complained of back pain in August 2007 and was subsequently hospitalized in September 2007. He reported having smoked about 40 cigarettes a day for at least 25 years before the age of 45 and had no family history of prostate cancer. Pathological diagnosis using a prostate needle biopsy was mixed small cell carcinoma and adenocarcinoma of the prostate. The small cell carcinoma showed positive staining for CD56, chromogranin A, and synaptophysin and mixed components of adenocarcinoma (Gleason Score 4+5=9) (Figure. 1). The clinical stage was T4N1M1 (primary prostate tumor with multiple osteolytic bone, liver, lymph node metastases), and laboratory values for serum PSA, pro-gastrin-releasing peptide (ProGRP) were elevated to 176.77 ng/ml and 544 pg/ml, respectively.

In September 2007, treatment with dual hormonal therapy using gonadotropin-releasing hormone (GnRH) agonist and oral androgen receptor antagonist was commenced. His serum PSA levels subsequently became undetectable and primary tumor and metastatic lesions showed marked

shrinkage. However, in October 2007, his serum ProGRP levels increased gradually up to 1,660 pg/ml and the primary tumor and metastatic lesions expanded. Consequently, the oral androgen receptor antagonist was discontinued and he was treated with the GnRH agonist concurrent with cisplatin plus etoposide targeting small cell carcinoma. This treatment regimen was effective and tumor regression of primary and respective metastatic tumors was observed. His serum ProGRP level was decreased to 40.2pg/ml.

In March 2008, he had a relapse with signs of meningeal irritation, including headache, frequent vomiting, and decreased level of consciousness, and he deteriorated quickly. In April 2008, he was re-hospitalized. His serum ProGRP level had increased again to 1,658 pg/ml; however his level of serum PSA was little changed. Magnetic resonance imaging (MRI) revealed multiple brain metastases and meningeal carcinomatosis, related with meningeal irritation. A lumber puncture was performed to collect a sample of cerebrospinal fluid (CSF) for analysis. Atypical cells with high nuclear/cytoplasmic ratio and coarse chromatin were detected (Figure. 2) and elevated ProGRP level (4,665 pg/ml) was revealed, although the PSA level was undetectable in the sample of CSF and a sample of serum. Therefore, small cell carcinoma of prostate, complicated

with meningeal carcinomatosis was diagnosed. However, time to progression was just one month after four cycles of previous combination chemotherapy and his performance status was decreased from 1 to 3. We recommended that he receive best supportive care, however, he and his family desired other treatment.

In May 2008, we commenced new combined therapy with carboplatin AUC5 (day1, monthly) plus irinotecan 60mg/m^2 (days 1,8 and 15, monthly), which is the most common 1st line treatment in patients with extensive-stage small cell lung carcinoma. On day 13 after initiation of the therapy, Grade 4 febrile neutropenia emerged and he was treated with G-CSF for 5 days and an anti-biotic agent for 7 days. His symptoms disappeared by day 20 and his status recovered to PS1. Similarly, the multiple brain metastases and meningeal carcinomatosis were dramatically diminished in MRI (Figure. 3), and serum ProGRP level was decreased to 134.8pg/ml in July 2008. Subsequently, his condition was maintained by chemotherapy (irinotecan alone from July 2008 because of the G4 adverse events) and hormonal therapy for 5 months after the induction of 2nd line chemotherapy in May 2008. The clinical course of this case is demonstrated in Figure. 4.

Discussion

Meningeal carcinomatosis in prostate cancer is relatively rare. The incidence has been reported as less than 5 % in patients with prostate cancer, particularly in those with terminal stage [4]. The gold standard for diagnosis of meningeal carcinomatosis is dependent on cytological examination of malignant cells in CSF. Unfortunately, false-negative results are common, and the positive rate for all types of tumors is around 50~60% with one sample, 80% with two, and 90% with three [5]. However, even multiple CSF samples may fail to yield an accurate diagnosis leading to protracted clinical uncertainty for some patients. It has been speculated that the cause of false-negative cytology may be the obstruction of CSF flow, inadequate amounts of CSF, or delayed handling of cytology specimens [6].

Of imaging methods, gadolinium-enhanced MRI has high sensitivity and specificity to abnormal findings with meningeal carcinomatosis, although a false-negative rate of up to 30% has been reported [7]. In the present case, gadolinium-enhanced brain MRI clearly presented enhancement of the meninx along the cerebral sulci, and these findings were useful for evaluation of abnormal findings and clinical courses. However, imaging methods alone cannot

render a definitive diagnosis. Therefore, a novel surrogate marker is needed for the diagnosis of meningeal carcinomatosis and it is extremely important to define the cancer type as well as the presence of any malignancy, e.g. differential diagnosis of double primary cancer or mixed type cancer.

Recently, ProGRP was reported to be a useful and sensitive marker for SCCP as well as small cell lung cancer (SCLC) [8]. Pedersen *et al.* demonstrated that elevated level of ProGRP in CSF is useful to diagnose meningeal metastases of small cell carcinoma [9]. Castro MP *et al*. reported a case with small cell carcinoma of unknown primary site, in which the ProGRP level in CSF was elevated by more than six orders of magnitude above the serum level despite repeated negative CSF cytologic results. Extensive meningeal carcinomatosis was demonstrated by autopsy [10]. In the present case, the ProGRP level in CSF was elevated to 4,665 pg/ml, almost three orders of magnitude above the serum level (1658 pg/ml). Thus, diagnosis of meningeal carcinomatosis in patients with SCCP may be established by elevated ProGRP levels in CSF samples. To our knowledge, this is the first report of SCCP with meningeal carcinomatosis monitored by elevated ProGRP level in CSF as well as in serum.

Hormone therapy for SCCP is ineffective except for mixed type with

adenocarcinoma [11]. Current recommended chemotherapy regimens for SCCP are platinum based, similar to SCLC, because SCCP demonstrated similarity to SCLC in morphologic features [12] and expression phenotype pattern of some genes [13]. Of those, combined chemotherapy with cisplatin plus etoposide is the most common. A phase II trial of doxorubicin combined with this regimen for SCCP showed more toxicity, but not longer survival [2]. Other reports showed that amrubicin or combination chemotherapy with gemcitabine, docetaxel, and carboplatin regimen may be alternative candidates for first induction chemotherapy for patients with SCCP [7, 14].

Chemotherapy has been of limited role in patients with brain metastases because of blood brain barrier (BBB). Candidate CNS-acting drugs have the poorest success rate and more than 98% of such drugs cannot cross BBB [15]. In patients with glioma, carboplatin was detectable in CSF beginning 0.5 Hr after the initiation of infusion and was then slowly eliminated. The mean maximum CSF concentration of carboplatin was 15.25% of that in plasma [16]. In preclinical studies, irinotecan has demonstrated cytotoxic activity against central nervous system tumor xenografts [17]. Combined chemotherapy with carboplatin and irinotecan was an effective treatment for SCLC brain metastases [18].

We chose combined chemotherapy with carboplatin plus irinotecan for this refractory case with meningeal irritation, in consideration of his poor performance status and relapse at only 1 month into treatment with cisplatin and etoposide. Fortunately, he responded favorably to treatment and showed improved quality of life and performance status.

In extended disease (ED) of SCLC, cisplatin plus irinotecan was compared with cisplatin plus etoposide in a randomized phase III trial and showed a better survival rate for patients with good performance status [19]. In contrast, carboplatin is known to have activity similar to cisplatin but exhibit a more favorable toxicity profile and is widely used as a practical substitute for cisplatin in ovarian cancer and ED-SCLC. Until now, the combination chemotherapy of carboplatin and irinotecan has shown to be a convenient, tolerable, and effective treatment in several phase II trials of untreated SCLC in extensive stage [20, 21]. In addition, high efficacy in carboplatin and irinotecan has been demonstrated in phase II trials for refractory or relapsed SCLC patients [22, 23].

In the present study, we report a rare case of SCCP complicated with meningeal carcinomatosis in which combined treatment with carboplatin plus irinotecan was effective. Therefore, this combined regimen could be promising for patients with

relapsed meningeal carcinomatosis with poor performance status or old age.

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Figure Legends

Figure 1.

Histological findings of a small cell carcinoma component in prostate: Carcinoma cells proliferate in solid (left) and trabecular (right) patterns. Carcinoma cells have coarse chromatin and dark nuclei. Nuclear/cytoplasmic ratios are high (A). Histological findings of an adenocarcinoma component in prostate: Carcinoma cells have irregular glandular structures (B). Immunostaining: Synaptophysin is diffusely positive for small cell carcinoma (C). A, B, H&E, x400; C, Immunostaining of synaptophysin, X200.

Figure 2.

Cerebrospinal fluid cytology: Cohesive atypical cells with high nuclear/cytoplasmic ratio and coarse chromatin are shown. A mitotic figure can also be observed in this field. X400

Figure 3.

Gadolinium-enhanced brain MRI: Multiple brain metastases (arrows) and meningeal enhancements due to carcinomatosis (straight arrows) were

observed in April 2008 (A). However, these findings improved following treatment with chemotherapy in August 2008 (B).

Figure 4.

Clinical course of chemotherapy for small cell carcinoma of the prostate: Trends in serum ProGRP and serum PSA levels.

Figure 1.

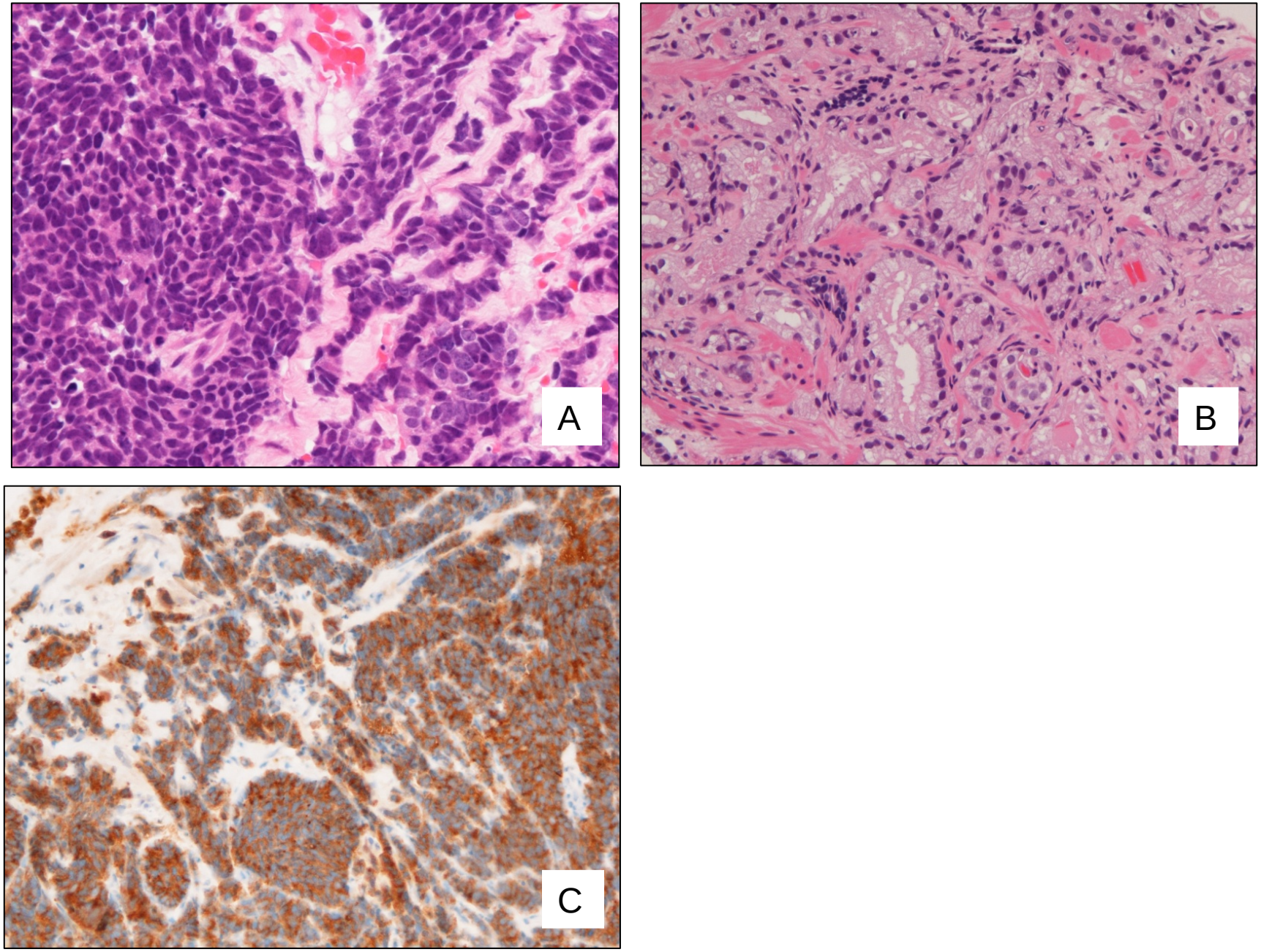


Figure 2.

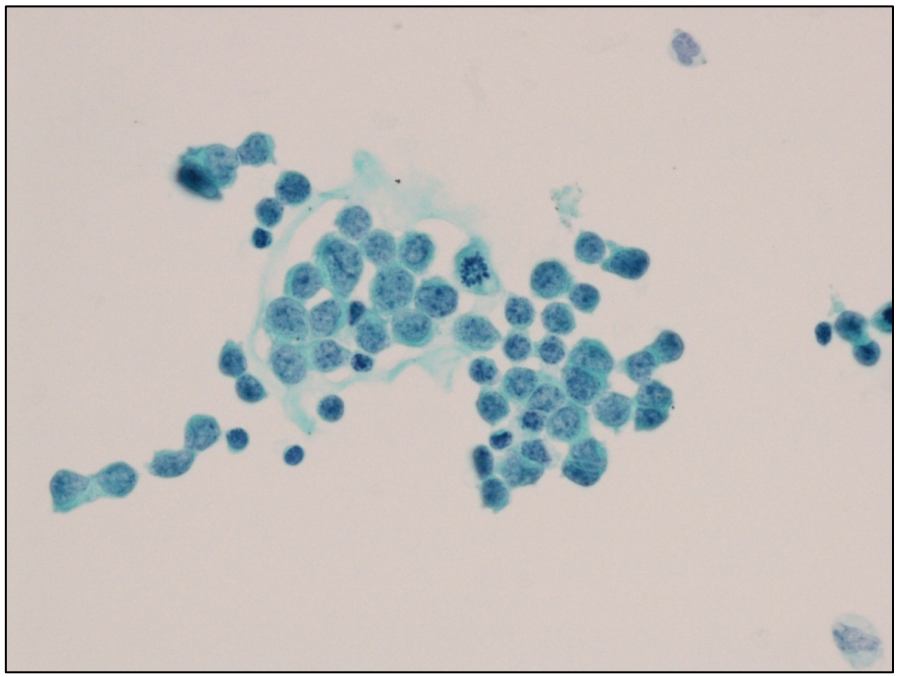


Figure 3.

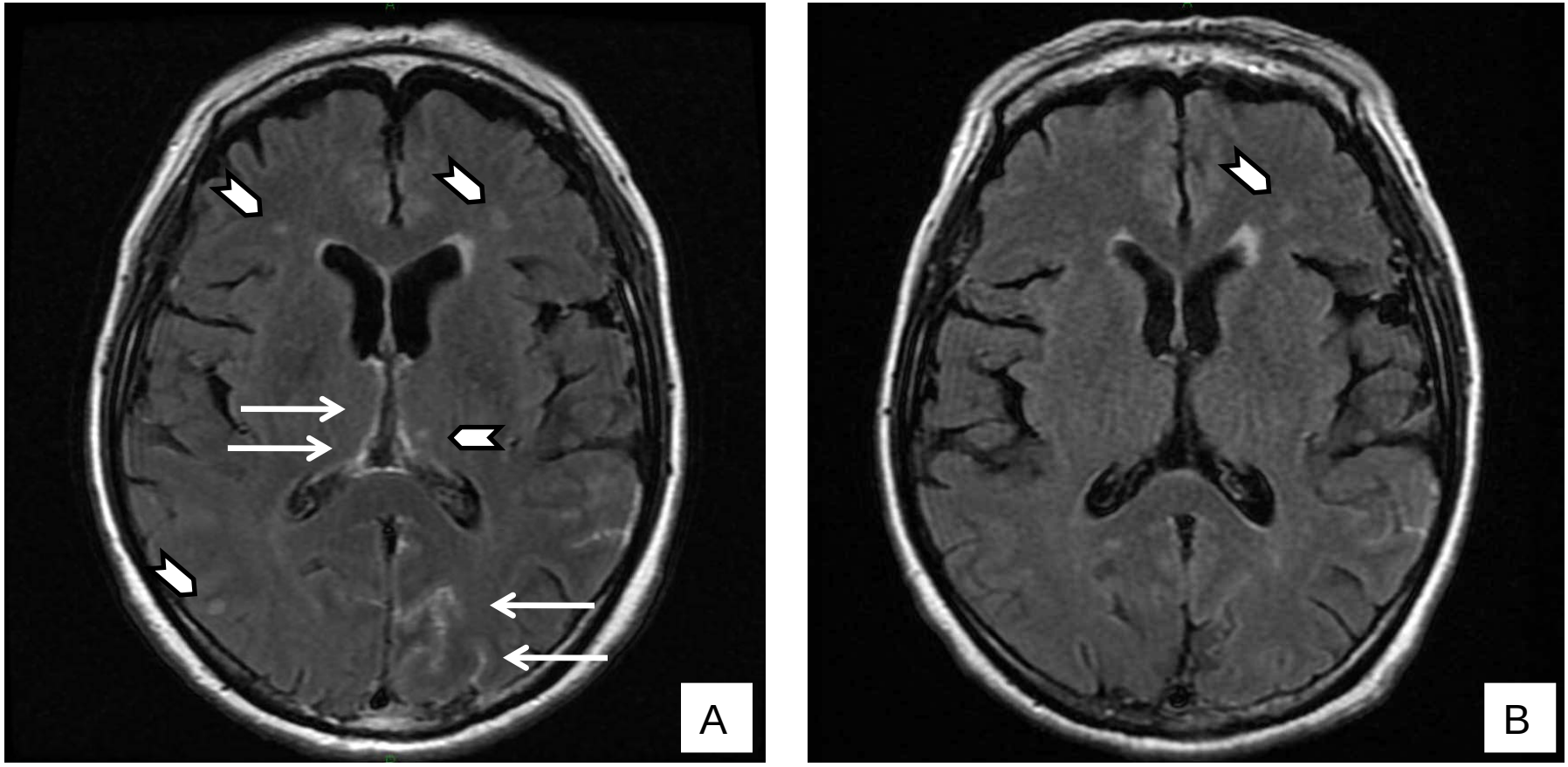
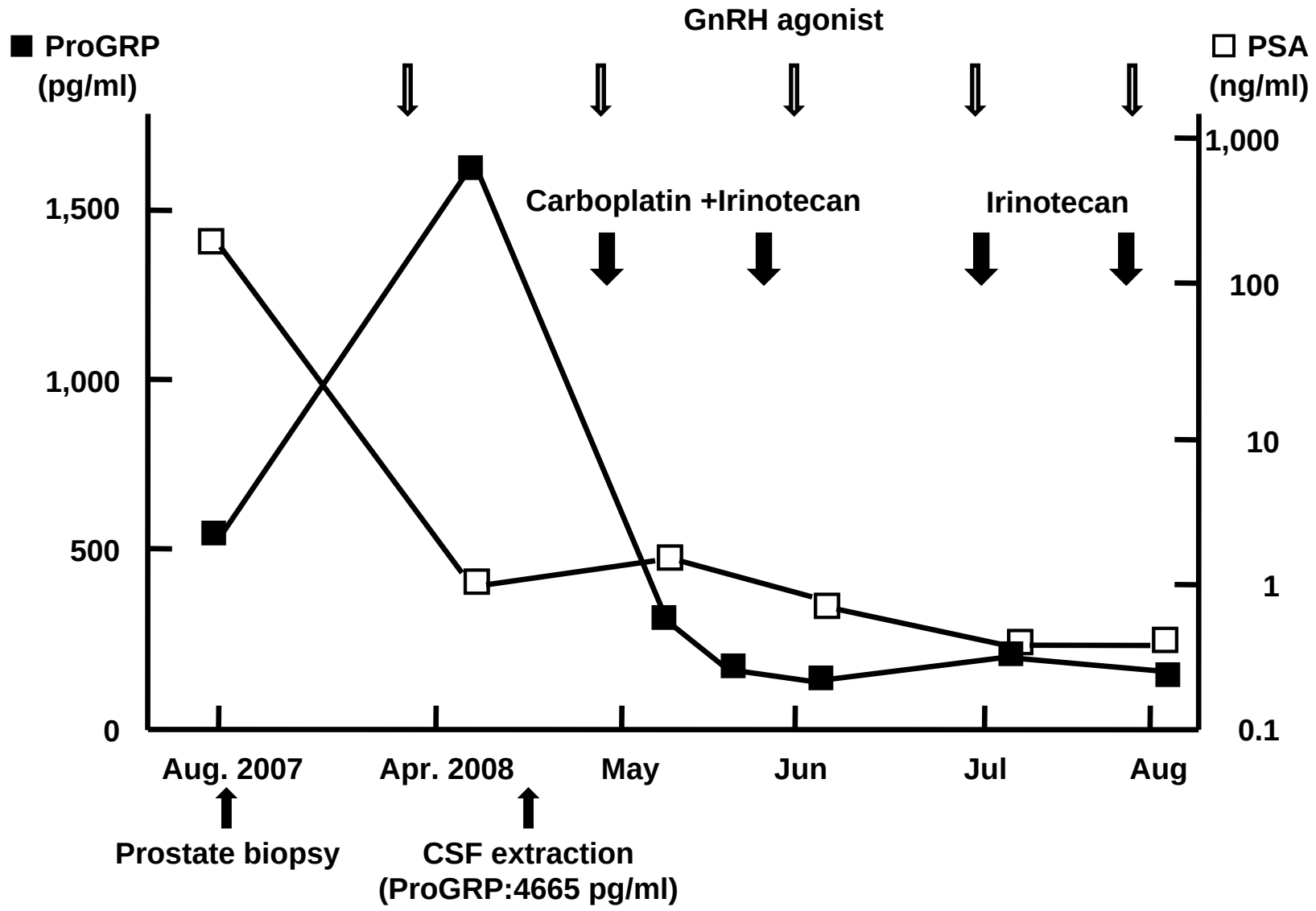


Figure 4.


GnRH agonist
ProGRP
(pg/ml)
PSA
(ng/ml)
Carboplatin +Irinotecan
Irinotecan
1,500
1,000
500
0
1,000
100
10
1
0.1
Aug. 2007
Apr. 2008
May
Jun
Jul
Aug
Prostate biopsy
CSF extraction
(ProGRP:4665 pg/ml)