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A Case of Prostate Cancer with Multiple Bone Metastases in which Standard Treatment was Ineffective but Remission was Achieved with Amplified Natural Killer Cell Therapy, and the Usefulness of PD-L1 Positivity as a Biomarker for Solid Tumors

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1. Abstract

Amplified natural killer (ANK) therapy is a treatment that improves the safety and efficacy of the original (LAK) immunotherapy. It is a method of extracting natural killer (NK) cells from the patient's own blood, culturing and amplifying them, enhancing their ability to specifically attack cancer, and returning them to treatment. In theory, it is effective for all cancers. The author has experienced and reported cases in which ANK therapy was significantly effective for ATL and malignant lymphoma. In this report, we report a case in which ANK therapy was effective for an elderly patient with multiple bone metastases from solid cancer prostate cancer, and all multiple bone metastases improved, and PSA also improved. Chemotherapy is the main treatment for patients with advanced solid cancers, and elderly patients, patients with renal failure, and patients with heart failure cannot be treated. ANK therapy is considered to be very effective not only for ATL cases, but also for some solid cancer cases, but there are cases where it is extremely effective and cases where it is not. Considering the mechanism of action of ANK therapy from case histology and research reports, it is effective against ATL, which has a large number of PD-L1-positive tumor cells, because it effectively kills PD-L1-positive tumor cells. Some solid cancers, such as lymphoma, gastric cancer, lung cancer, breast cancer, and prostate cancer, have many PD-L1-positive tumor cells. In this case, tissue staining confirmed that PD-L1 was positive as expected. By using PD-L1 as a biomarker and treating those with high levels, it may be possible to provide a more effective, safer treatment with fewer side effects than existing treatments. This is the first report to prove that PD-L1 positivity can be a biomarker for the effectiveness of ANK therapy.

2. Introduction

Amplified natural killer (ANK) therapy is a method of removing natural killer (NK) cells from the patient's own blood, culturing and amplifying NK cells to specifically enhance their ability to attack cancer, and returning them to the patient for treatment. It is generally effective against all cancers. In 1985, Rosenberg et al of the National Cancer Institute (NCI) performed a treatment called lymphokine-activated killer (LAK) immunotherapy[1]. A large volume of blood of about 50 L was extracted from the patient over 5 days in a week, and lymphocytes were extracted and cultured with rIL-2 for 3 to 4 days to induce LAK cells. These cells were

then transfused back to the patient. This treatment has shown some effects, but it is not common due to its high cost and strong side effects. The next instance where this therapy was performed was in Japan in the 1990s. However, the amount of blood collected was less than one-tenth of that collected by Rosenberg et al. Moreover, the expected effect was not achieved because the number of NK cells with a strong anticancer activity was low[2]. ANK immunotherapy focuses on the fact that among the various lymphocytes, NK cells have a strong anticancer effect. The amount of blood collected in the studies was about 5 L; however, by increasing the number and activity of NK cells before returning them to the patient, it is possible to obtain a safe and therapeutically useful effect[3].

In 1853, J. Adams, a surgeon at the London Hospital, reported the first case of prostate cancer detected by histological examination and described the condition as «a very rare disease.» [4]. In Japan, prostate cancer with bone metastasis was first reported in 1916. [5] Prostate cancer became known in the late 19th century. Surgery and treatment methods began to be explored, and initially surgical treatment was the main method.

Since the 1950s, hormone therapy for prostate cancer has been developed, expanding the treatment options and radiation therapy has also begun to be used.

The incidence and mortality rates of prostate cancer vary greatly by region. The incidence rate is particularly high in Western countries (North America, Europe), with the highest incidence recorded in African-American men. In Asian countries (Japan, China, etc.), the incidence rate is relatively low, but in recent years, it has been increasing due to the Westernization of diet and changes in lifestyle. As of 2017, prostate cancer is the most prevalent cancer in Japan. The risk of prostate cancer increases with age, especially in men over 50 years old. Men over 75 years old are significantly more likely to develop prostate cancer. Prostate cancer is strongly associated with family history, and if a father or brother has prostate cancer, the risk is two to three times higher. In addition, mutations in the BRCA1/BRCA2 genes are known to be risk factors. As of 2017, prostate cancer is the most prevalent cancer in Japan. [6]Drug treatment of prostate cancer began with the discovery of endocrine therapy, followed by the development of chemotherapy using anticancer drugs. The concept of removing male hormones (androgens) to control prostate disease was formed in the early 20th century through observations of animals such as dogs. In 1941, Charles Huggins and Clarence Hodges showed that when patients with metastatic prostate cancer underwent surgical castration by orchiectomy, their serum acid phosphatase levels, which had been abnormally high, returned to normal within about four weeks, and their pain and discomfort improved [7]. In the same year, Huggins et al. reported that oral administration of female hormones (estrogen) for drug castration was also effective in treating patients with advanced prostate cancer [8]. In 1975, the program reported subjective improvement and minimal toxicity in the first national randomized study of 5-fluorouracil versus cytoxan versus standard therapy. [9] Since then, numerous single-agent phase II trials have been conducted to test numerous chemotherapy regimens in patients with advanced prostate cancer, but these single-agent trials have generally only observed response rates of less than 10%.[10] Recent studies have used the decline in serum PSA as the primary indicator of treatment efficacy, and using this criterion, many chemotherapy combinations have reduced serum PSA levels by 50% or more in a significant proportion of patients. Agents such as corticosteroids, estramustine, doxorubicin, and the taxanes paclitaxel and docetaxel have been tried and have proven effective.

In 1979, prostate-specific antigen (PSA) was discovered and reported to be a potentially useful serum marker for prostate cancer. 21 Measurement of PSA levels was soon approved in the United States to monitor prostate cancer progression and response to treatment, and later as a prostate cancer screening test. [11]

Diagnosis is by rectal examination to measure size and hardness, and if there is any abnormality, PSA is measured. If the value is high, imaging such as MRI and a biopsy are performed to make a diagnosis. A diagnostic flow chart is shown in (Figure.1).

Advances in diagnostic imaging using MRI have made it easier to identify prostate cancer patients with high PSA levels who need treatment, and it is now recommended that MRI be performed before biopsy. Furthermore, the establishment of MRI/US fusion biopsy technology, which combines MRI images and real-time ultrasound, has reduced the number of cancers missed and eliminated unnecessary biopsies. [12]

Treatment methods include surgery, radiation therapy, hormone therapy, chemotherapy, etc. In terms of prognosis, the survival rate is high compared to other cancers. With early detection and treatment, the 10-year survival rate can be expected to be over 80%, but if distant metastasis occurs and the disease reaches Stage IV, the 5-year survival rate drops to approximately 60%.

If the disease progresses and multiple metastases occur, it is very difficult to extend the patient's life expectancy.

We report a case in which ANK therapy was effective in an elderly patient with prostate cancer who had not responded to existing hormone therapy and chemotherapy, had multiple bone metastases, and had a very poor prognosis.

3. Cases

The patient was a 75-year-old man who was diagnosed with prostate cancer and bone metastasis in May 2011 (Figure 1A, B, C). Bone scintigraphy showed abnormal accumulations of cancer cells in the left ilium, sacrum, left pubic acetabulum, and right pubic bone, suggesting bone metastasis. The PSA level was 27.3. Hormone therapy (Casodex and Leuprorelin every 3 months) was started in June, and the PSA level improved temporarily. However,

CT and bone scintigraphy in July 2014 showed the progression of multiple bone metastases (Figure 2A, B). ANK therapy was started in September 2014, and NK cells were collected 12 times (Figure 3). Bone scintigraphy showed improvement in all bone metastases, and the PSA level also normalized. Hormone therapy alone was continued, but no recurrence was observed, so hormone therapy was discontinued in August 2015 (Figure 4A, B). Seven years have passed since then, and the patient has been stable with no recurrence (Figure 5A, B). Subsequently, PD-L1 staining was performed on the tissue diagnosed as prostate cancer, and the result was positive (Figure 6).

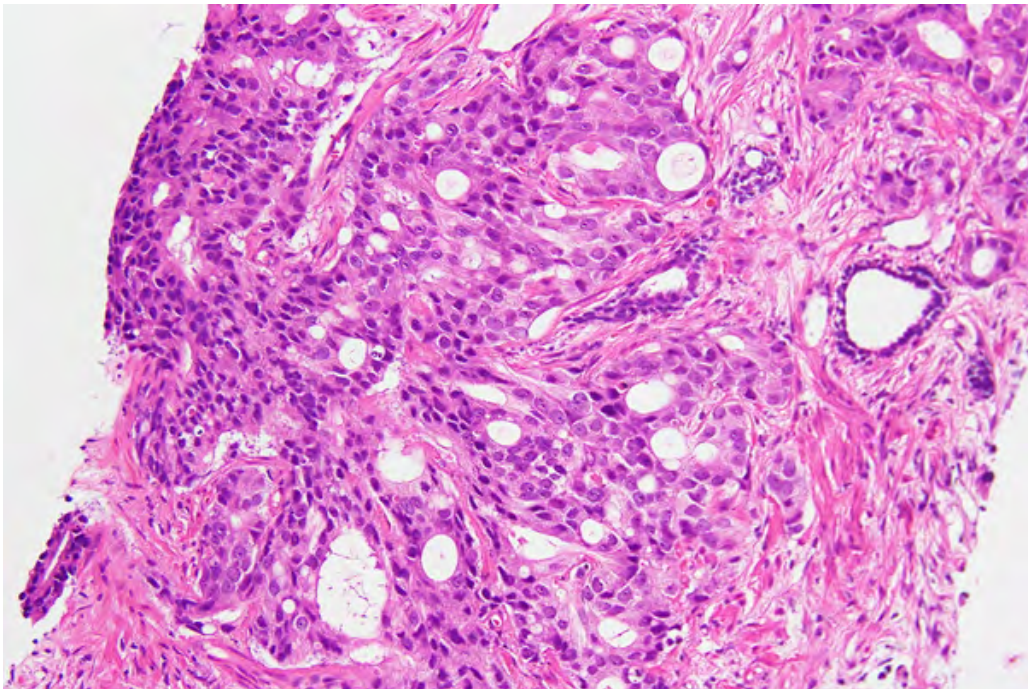

Figure 1A: HE ×200 Prostate cancer diagnosed

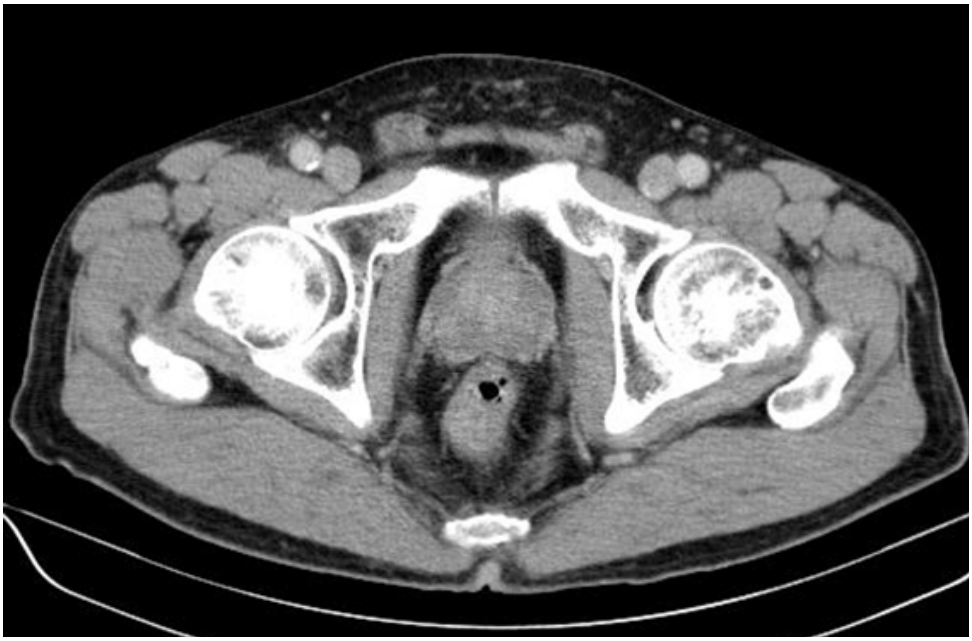

Figure 1B: May 2011: There is prostate enlargement, which is the primary focus, and prostate cancer is present.

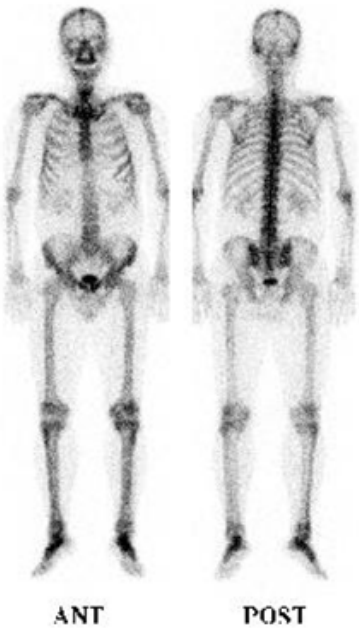

Figure 1c: May 2011: Bone scintigraphy showed abnormal accumulation of cancer cells in the left ilium, sacrum, left pubic acetabulum, and right pubic bone.

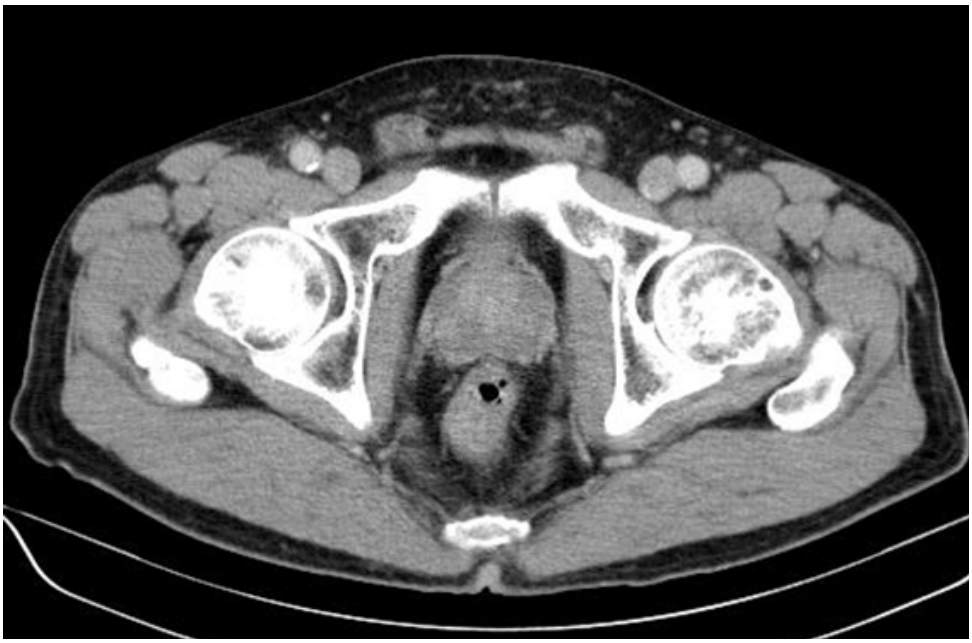

Figure 2A: July 2014: Primary prostate tumor growth is observed

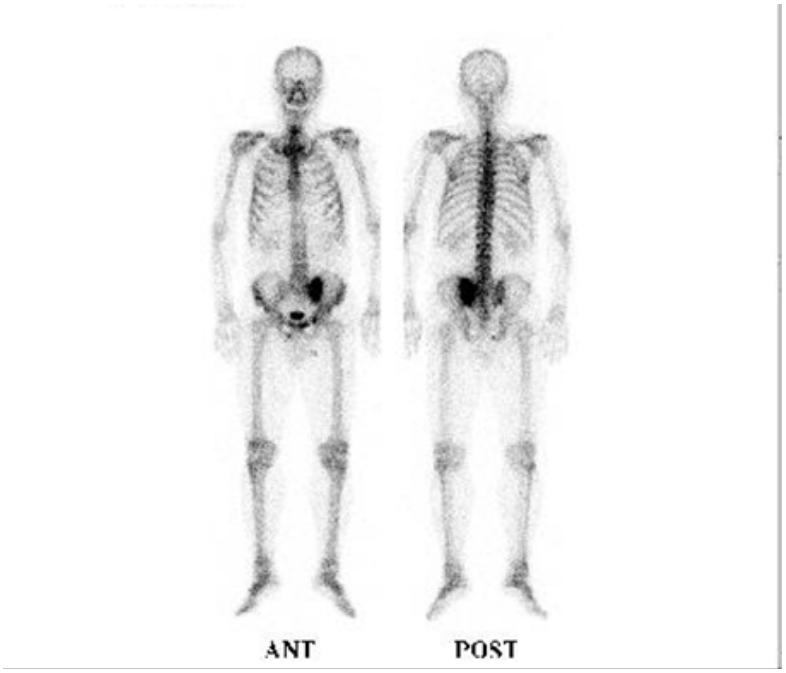

Figure 2B: July 2014: Worsening of bone metastases observed

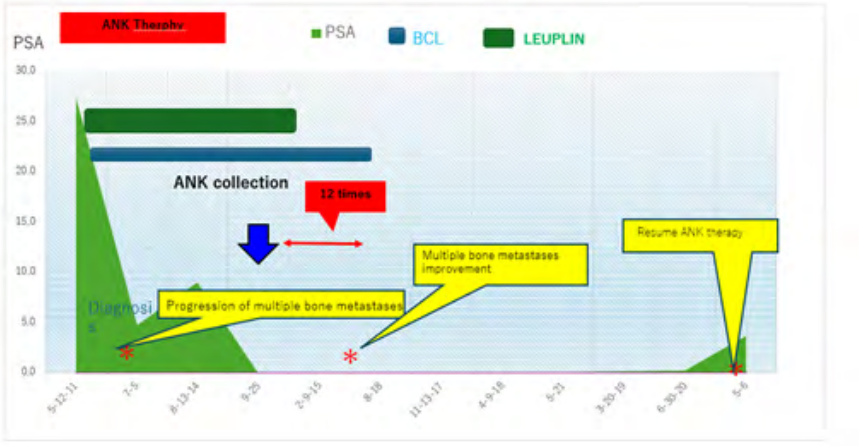

Figure 3: Prostate cancer treatment progress and changes in PSA

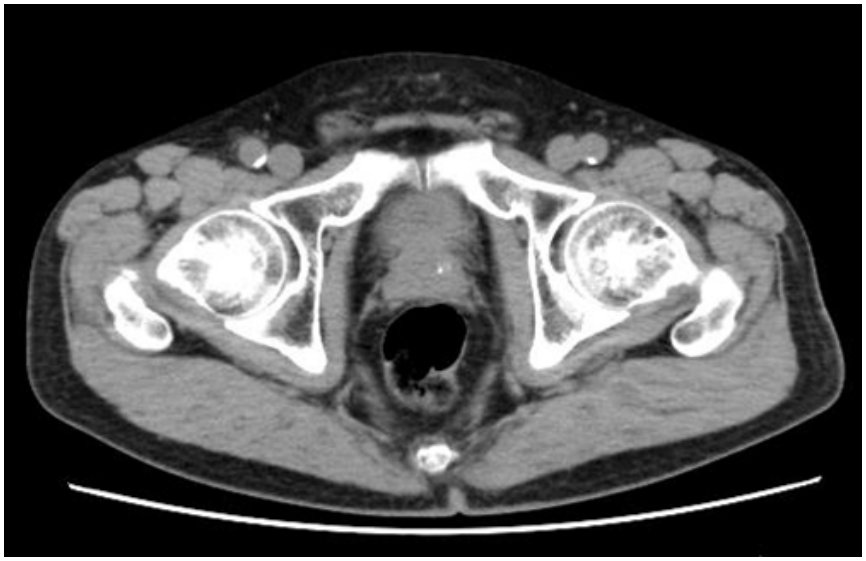

Figure 4A: September 2014: The primary prostate tumor is shrinking

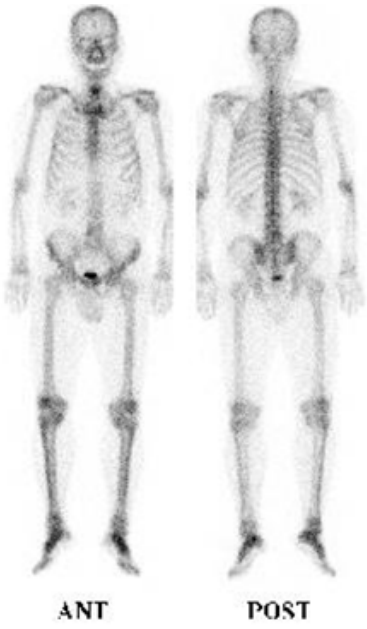

Figure 4B: September 2014: Bone metastasis showed remission

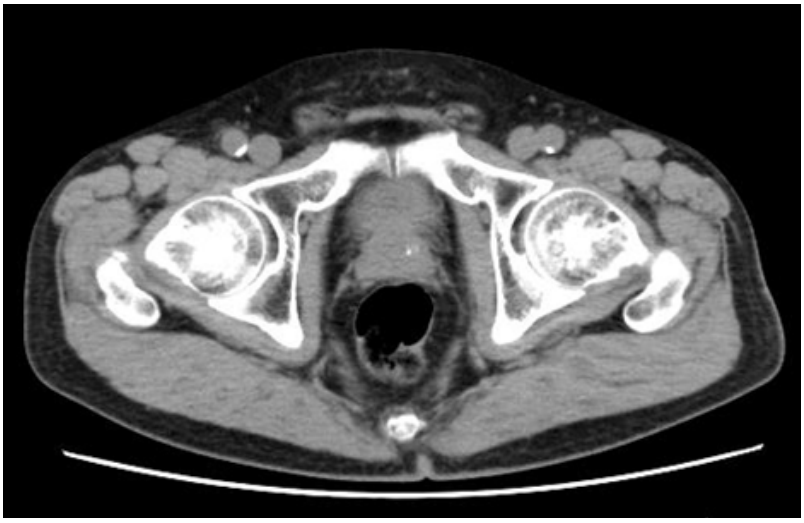

Figure 5A: August 2015: Prostate enlargement continues to improve

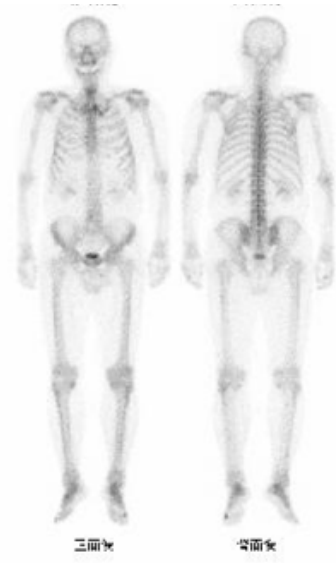

Figure 5B: August 2015: Bone metastasis remains in remission

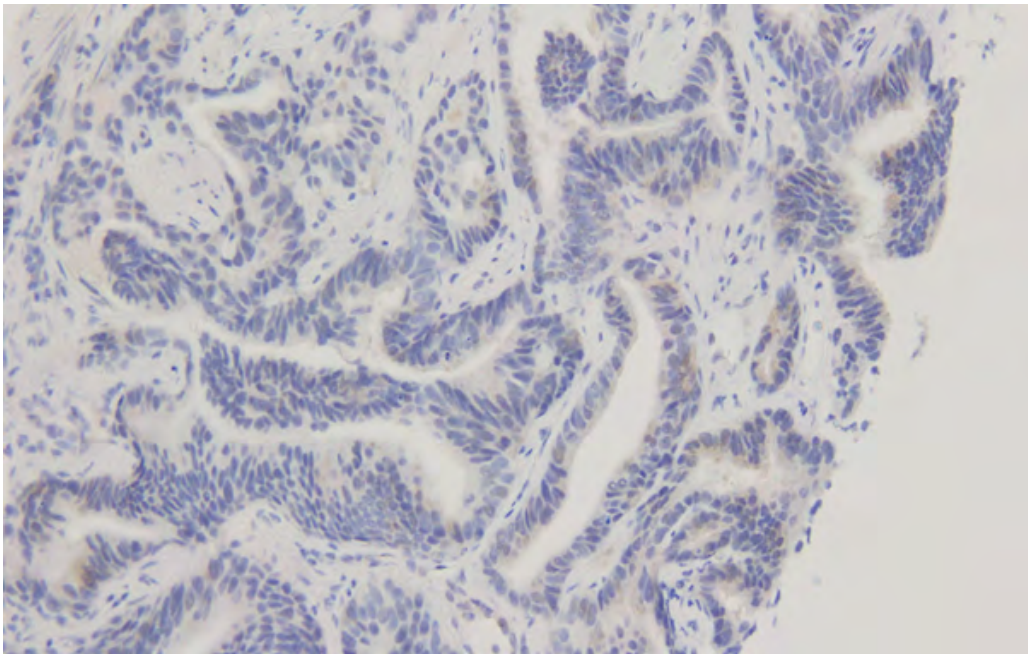

Figure 6: PD-L1 IHC 28-8 pharmDx ×200 Brown PD-L1 positive cells are generally observed in the cytoplasm of tumor cells.

4. Discussion

The ANK therapy used this time is completely different from the conventional immunotherapy for which the lymphocyte bank has technology, and it is involved in the production of ANK cells. ANK therapy is a treatment method in which approximately 5 L of blood is collected from the patient, the activated NK cells are amplified, and returned to the patient. For detailed culture and production methods of ANK cells, please refer to the papers [13,14]. The reason his ANK therapy was effective in these two cases is that ATL leukemia cells express NK cell co-stimulatory molecules such as CD80 and CD137L. ATL cells have regulatory T cell characteristics, and ATL patients are immunosuppressed. From this, it is clear that ATL cells express both stimulatory cofactors and inhibitory factors such as PD-L1. It has been reported that NK cells, which are extracted from blood, cultured and activated, can attack tumors regardless of tumor suppressor gene expression, unlike T cells [15].

For this reason, ANK therapy is specific to tumor cells and has a low risk of causing significant damage to the normal immune system. With this treatment, ATL patients do not experience the severe side effects seen with anti-CCR4 [16,17] or anti-PD-1 therapy [18]. High expression of PD-1 in ATL cells has also been reported [19]. Therefore, anti-PD-1 antibodies may inhibit the negative autoregulatory signals via PD-1 and PD-L1 in ATL cells and induce the proliferation of ATL cells. In ATL, PD-L1 may function as both an immunosuppressant for ATL cell proliferation and for the normal immune system. It is important to suppress PD-L1. It has even been reported that a large number of ANK cells kill PD-L1-positive tumor cells . [20] These results suggest that repeated administration of NK cells, including ANK cells, relieves immunosuppression via the PD-1-PD-L1 pathway. The manifestation of clinical outcomes in ATL often occurs only after a long latency period and continues into old age. It is known that the percentage of NK cells with the CD16+CD56+ phenotype is significantly lower in HTLV-1-infected carriers, and therefore administration of activated NK cells in the form of ANK therapy is believed to be effective [21] [22] [23]

In addition, other cancers with genomic abnormalities similar to ATL are often seen, such as diffuse large cell lymphoma, gastric cancer, esophageal cancer, and cervical cancer. ANK therapy for ATL is considered to be highly effective. [24]There are cases in which ANK therapy is very effective, such as the solid cancer prostate cancer reported in this study. From this, it is thought that ANK therapy may be highly effective against cancers with high PD-L1 expression, killing PD-L1-positive tumor cells. In the case of solid cancers, PD-L1 levels can be said to be a biomarker that predicts the effectiveness of treatment. By using biomarkers to narrow down the target cancer, it may be possible to provide a more effective and safer treatment than existing anticancer drugs and immunotherapy. In this case, to prove this, PD-L1 immunostaining was performed on the tissue diagnosed as prostate cancer, and it was positive. It is believed that ANK therapy worked remarkably according to the mechanism described above. Up to this point, the effectiveness has varied depending on the case of solid cancer. It has been suggested that measuring the PD-L1 positivity rate from cancer tissue can be a biomarker for the effective use of ANK therapy. [25]

5. Conclusion

ANK therapy is completely different from existing immunotherapies. By amplifying activated NK cells, it can attack without

narrowing down the target, and it has few side effects. Previous reports have proven that ANK therapy is more effective than existing treatments for blood cancers such as ATL and malignant lymphoma, and has overwhelmingly fewer side effects. It is known that ANK therapy is effective through two mechanisms that suppress PD-L1, and previous research has suggested that ANK therapy may be highly sensitive and effective even in solid tumors if the cancer has many PD-L1-positive tumor cells. In this case of prostate cancer bone metastasis, ANK therapy was highly effective after confirming the presence of many PD-L1-positive cells.

These reports show that ANK therapy is effective not only in blood cancers but also in solid cancers, and by using PD-L1 as a biomarker, it is possible to select cases with high therapeutic effects and perform treatment more safely.

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8. Declaration of Conflicting Interests

The authors have no conflicts of interest to declare.

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