

Case Report

The Alkaline Phosphatase Flare Phenomenon: A Transient Substantial Increase in Alkaline Phosphatase Concentration in a Prostate Cancer Patient after Starting GnRH Agonist Treatment

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Keywords

Alkaline phosphatase · Flare metastatic prostate cancer · GnRH agonist

Abstract

A 78-year-old man with metastatic prostate cancer was referred to the hospital 5 weeks after the initiation of systemic therapy with goserelin (GnRH agonist) because of a significant increase in alkaline phosphatase (ALP) concentration despite clinical improvement. Further workup revealed a decrease in prostate-specific antigen levels and a lack of radiological signs of disease progression. Subsequently, the ALP dropped spontaneously. This case report is an example for an early ALP flare after initiation of endocrine therapy in patients with bone metastasis which is consistent with a treatment response. Clinicians should be familiar with the ALP flare phenomenon in this setting, which does not reflect disease progression or treatment failure, in order to prevent unnecessary investigations, hospital admissions, or even erroneous termination of successful therapy.

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Introduction

Alkaline phosphatase (ALP) is an enzyme expressed on the surface of osteoblasts [1] and contributes to bone mineralization. Consequently, it is used as a marker of osteoblast activity. However, surface expression has also been demonstrated in metastatic prostate cancer (PCa) cells [2, 3]. In men with advanced PCa, the skeleton is the most common site of metastatic disease [4]. In the bone, PCa cells may contribute in two ways to an elevated ALP level: by

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activating osteoblasts and by expressing tumor-derived ALP. Hence, the measurement of ALP may be used for the diagnosis of bone metastasis and the monitoring of treatment response. Higher ALP levels are associated with disease progression and early death [5]. However, increased bone turnover and repair may also be reflected by elevations in ALP concentrations. There are several other diseases and conditions associated with an increase in ALP levels such as cholestatic liver diseases, bone disorders, and drug toxicity. In this regard, the bone-specific ALP may be used to differentiate ALP elevations secondary to bone disorders from those caused by liver diseases [6]. Monitoring ALP concentration may be advantageous as it is a widely available and inexpensive, sensitive, and noninvasive method for detecting bone metastatic cancer compared with computed tomography (CT) or bone scans. During treatment, dynamic changes in ALP appear even earlier than changes in prostate-specific antigen (PSA) [7].

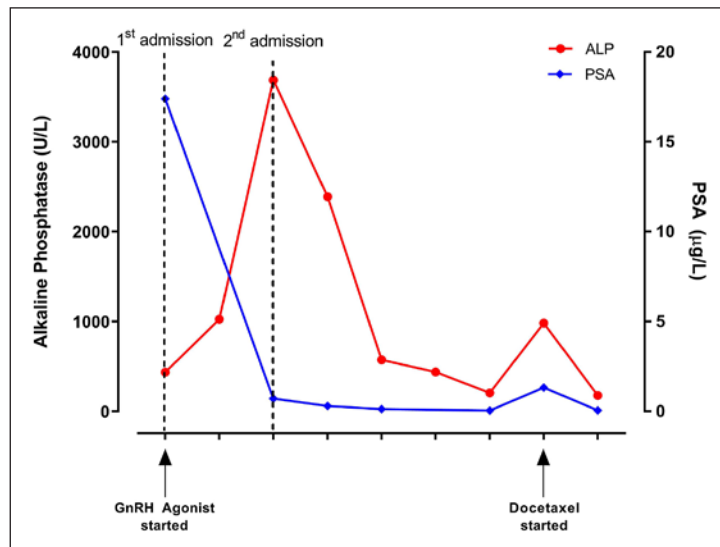
A transient elevation in the ALP concentration 4–6 weeks after initiation of systemic treatment may be observed in patients with bone metastasis of various malignancies. This phenomenon is called ALP flare, which may be defined as a transient increase in the serum ALP level to 120% or more of the pretreatment value, followed by a subsequent decrease [8]. A remarkable variety of duration and intensity of ALP flares has been reported in previous studies, possibly related to the lack of a generally accepted definition of this phenomenon [5, 8–10]. A transient elevation in ALP has been observed in patients after the initiation of epidermal growth factor receptor-tyrosine kinase inhibitor treatment for non-small-cell lung cancer as well as after the start of systemic therapy in patients with advanced breast and PCa with bone metastasis [9, 11]. These phenomena should not be interpreted as a sign of treatment failure but rather as treatment response, and anticancer therapy should be continued [8, 11, 12].

Case Report

A 78-year-old man was referred to our hospital by his primary care physician because of a marked increase in ALP. The patient had been diagnosed with metastatic PCa (Gleason score 7, lymph nodes and bones) during a previous admission 5 weeks earlier. Treatment with the GnRH receptor agonist goserelin and the antiandrogen bicalutamide (transient treatment for 2 weeks to prevent a testosterone surge) was initiated.

On admission, the patient reported feeling much better than before the initiation of therapy, and his walking distance had markedly improved. Physical examination remained unchanged compared to the previous admission, as was his medication list. Laboratory results were significant for an 8.4-fold increase in ALP concentration from 437 to 3,688 U/L (normal range 40–130 U/L) (Fig. 1) in the absence of changes in other liver function tests. On the contrary, his PSA levels had dropped significantly from 17.4 to 0.17 µg/L (normal range <4.1 µg/L). A CT scan of the abdomen revealed stable metastatic disease without any signs of progression. Bone-specific ALP levels were markedly elevated (1,060 µg/L, normal range 5.5–24.6 µg/L) and the bone turnover marker C-terminal telopeptide (beta-CrossLaps) had significantly increased from 0.7 during the first admission to 3.1 ng/mL (normal range 0.13–0.46 ng/mL). These results ruled out cholestatic liver disease or drug-related hepatitis as a cause of the elevated ALP. Given the clinical improvement and decrease in PSA levels, an ALP flare as a consequence of endocrine therapy was diagnosed, treatment with goserelin was continued, and the patient was discharged immediately. Subsequently, ALP and PSA concentrations decreased spontaneously (minimum ALP and PSA concentration 206 U/L and 0.14 µg/L, respectively).

Fig. 1. Course of ALP and PSA since the start of androgen deprivation therapy with goserelin (GnRH agonist). ALP, alkaline phosphatase; PSA, prostate-specific antigen.



Eight months later, the patient was again admitted because of dizziness and weakness with a consequent fall at home during continued therapy with goserelin. He did not report any pain, and physical examination was unchanged. Laboratory results were significant for a raise in ALP concentration (980 U/L) with a mild but significant increase in PSA concentration (1.32 µg/L). Progression of bone and lymph node metastases was evident on CT scan of the abdomen and a bone scan. After discussing the therapeutic options with the patient, palliative chemotherapy with docetaxel and low-dose dexamethasone was initiated. He reported a remarkable improvement of dizziness and fatigue after the beginning of chemotherapy. After 2 months of chemotherapy (approximately 1 year after the start of androgen deprivation therapy), the response to therapy was confirmed by CT and bone scan, with a concomitant drop in PSA and ALP levels (ALP 176 U/L, PSA 0.06 µg/L).

Discussion

In PCa patients, a transient increase in ALP concentrations (“flare”) is occasionally observed 4–6 weeks after initiation of endocrine treatment, in particular in the presence of metastatic disease and higher PSA levels [8]. While the exact mechanism remains to be elucidated, the observed ALP flare probably reflects increased osteoblastic activity (“bone repair”) in response to effective treatment. However, recognition of this phenomenon is important to avoid discontinuation of a beneficial treatment because of misinterpretation of the flare as a sign of disease progression or adverse drug event. Rather the opposite is true, as an ALP flare is a sign of treatment response [13]. As hepatic disease or drug toxicity may contribute to ALP elevations, measurement of bone-specific ALP may assist in differentiating an ALP flare from other medical conditions [3, 6]. This is of particular importance in the presence of discordant clinical and laboratory findings as shown in the present case. Despite his improvement in overall health and well-being, the patient was admitted because of concerns of disease progression and a lack of knowledge of this phenomenon.

The ALP flare phenomenon is well described in the literature, in particular in advanced PCa [5, 8, 13]. Compared to a phase III study of the GnRH receptor agonist leuprolide versus the GnRH receptor blocker degarelix by Schröder et al. [14], the ALP elevation in our case was

more pronounced (3,600 U/L vs. a mean of approximately 350 IU/L in the group of patients with metastatic disease and a hemoglobin level <13 g/dL) after 6–8 weeks. This is probably explained by a high tumor burden at the initiation of endocrine therapy in the present case.

The total Gleason score was previously identified as predictive of progression to androgen-independent PCa [15]. In line, the extraordinary rise in ALP in our patient with a moderate Gleason score of 7 was associated with early progressive disease, consistent with previous studies that identified an early ALP flare as a negative prognostic marker both after orchiectomy and GnRH receptor agonist treatment [5, 8]. Interestingly, in a recent retrospective study of PCa patients with skeletal metastasis receiving abiraterone treatment, an initial ALP increase within 4 weeks followed by a rapid decline to pretreatment levels within 8 weeks was associated with a reduced risk of disease progression at 12 weeks after initiation of abiraterone treatment [7]. However, in multivariate analysis only the absence of a >50% PSA reduction at 12 weeks was associated with disease progression and overall survival. This is possibly explained by the small number of patients limiting the power to show a difference in multivariate analysis for both variables. In addition, the study showed that ALP increase appears earlier than PSA decline and should lead to continuation of abiraterone.

Given the association of an ALP flare early after initiation of androgen deprivation therapy with a shorter progression-free survival in PCa [8], close surveillance or treatment intensification may be considered in these patients. Interestingly, in a retrospective analysis a significant increase in progression-free survival was only demonstrated in patients with an ALP flare within 4 weeks after orchiectomy who received additional chemotherapy compared to patients with orchiectomy but without chemotherapy [10]. Provided the mechanism of the ALP flare after orchiectomy is similar to that of the ALP flare after initiation of endocrine therapy, future studies should assess whether its occurrence may be used as a marker to initiate early additional chemotherapy in patients with PCa.

Conclusion

As shown in this case report, monitoring of ALP concentrations after the initiation of endocrine therapy may assist in identifying patients with a high risk of early disease progression, and may be used for individualization of follow-up and tailoring future treatment. However, the cutoff for a significant ALP flare associated with early progressive disease has yet to be determined, and clinical trials are required that evaluate treatment decisions based on the presence or absence of a significant ALP flare. Clinicians should be familiar with the ALP flare phenomenon, which may occur in patients with bone metastasis after initiation of treatment and does not reflect disease progression or treatment failure, in order to prevent unnecessary investigations or even admissions.

Statement of Ethics

The patient has given his written informed consent to publish his case.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

P. Merlo and M. Osthoff collected the data, performed the literature research, and wrote the first draft of the manuscript. C. Rochlitz assisted in writing and editing the manuscript. All authors were involved in the care of the patient and approved the final manuscript.

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