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Original article

Adrenomedullin predicts high risk and culture positivity in children with solid tumors suffering from neutropenic fever

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ABSTRACT

Aim of study: Neutropenic fever is a source of morbidity and mortality in children with cancer. It is not possible to detect the causative agent in cultures in most cases; the research for a marker that can show the severity of the disease is ongoing. We evaluated the role of adrenomedullin (ADM) at predicting prognosis on patients with febrile neutropenia, which has been proven to be a good prognostic marker for diseases with high morbidity and mortality, such as heart failure, ischemic ventricular dysfunction, sepsis, and systemic inflammatory response syndrome.

Materials and methods: We recorded the 36 febrile episodes of 14 children receiving chemotherapy due to solid tumors. There were 10 events with unknown origin in the low-risk group, while in the high-risk group, there were 17 events with unknown origin, 8 events with microbiological origin and 1 event with clinically proven infection. Cultures were positive only in the high-risk group. However, the changes of ADM levels through time periods (first, second, third, and seventh days) were not significant.

Results: The first-day plasma ADM levels significantly predicted the presence of culture positivity (AUC 0.628, 95% CI 0.40–0.85, $p = 0.303$) and high-risk patients with neutropenic fever (AUC 0.76, 95% CI 0.56–0.97, $p = 0.016$).

Conclusion: Our study showed that increased plasma ADM was correlated with high-risk neutropenic fever and culture positivity. The ADM levels in the high-risk group were clearly high at the diagnosis and continued to the end of the treatment.

1. Introduction

Fever is a well-known complication in neutropenic patients with cancer [1]. During neutropenia, fever may be the first and only clinical manifestation of infection. Because of high morbidity and mortality, evaluation of the source and severity of infection must be fast in a neutropenic patient. Antibiotics should be started as soon as possible. Beginning antibiotic treatments more than 1 h after the fever onset has been associated with highly adverse events such as in-hospital mortality [2]. Unless broad-spectrum, empirical antibiotic therapy is initiated within the first 24–48 h, the risk of septicemic mortality increases by 50–60% [3]. However, because the source of infection cannot be found in 75–80% of cases, and the suspected organisms grow in only 25–30% of cultures, empiric antibiotherapy is started immediately in most of cases [4–6]. The markers that can help to show the etiologic agent can be confounding because of the harmful effects of chemo- or radiotherapy. Therefore, a risk score system is commonly used to evaluate and treat the patient. However, there is still a need for new specific biomarkers.

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Adrenomedullin (ADM) is a peptide with 52 amino acids that is produced from cultured vascular smooth-muscle cells and vascular endothelial cells, and its production is generally augmented by inflammatory agents such as lipopolysaccharide, tumor necrosis factor and interleukin-1 [7]. Adrenomedullin has pleiotropic effects, including regulation of inflammation, infection, angiogenesis, mineralized tissue formation, and development [8–10]. It may be a predictor of subsequent organ failure and result in septic shock and urinary tract infection [11–13]. Adrenomedullin has been previously evaluated and found to be beneficial as a prognostic marker for high morbidity and mortality conditions such as heart failure, ischemic ventricular dysfunction, localized bacterial infection, sepsis, pneumonia, and systemic inflammatory response syndrome [11,14,15]. Thus, we aimed to evaluate the plasma ADM level in children with neutropenic fever during the first three days of treatment and again at the end of treatment for its efficacy as a useful marker for determining the severity of disease and predicting prognosis.

2. Material and methods

2.1. Subjects

In all, 36 febrile episodes of 14 patients receiving chemotherapy due to solid tumors between June 2011 and May 2013 were included in the study. Inclusion criteria for the patients included the following, according to national pediatric neutropenic fever guidelines: (1) single axillary temperature $\geq$ 38.0 °C, a temperature $\geq$ 37.5 °C for longer than 1 h, or two elevations > 37.5 °C during a 12-h period in neutropenic patients; (2) absolute neutrophil count (ANC) < 500 cells/μL or an ANC that is expected to decrease to <500 cells/μL during the next 48 h [16]. Rapid evaluation consisted of history, physical examination, and laboratory tests (Complete blood count CBC, biochemistry, urinalysis, central catheter peripheral blood and urine cultures, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and chest X-ray). Patients were divided into low-risk (LR) and high-risk (HR) categories, as described by Alexander et al. [17,18]. Patients were also divided into culture-negative (CN) and culture-positive (CP) groups. Patients were treated with individualized empiric antimicrobial monotherapy or combination therapy according to their risk category. Age, gender, diagnosis, duration from the last chemotherapy, Karnofsky performance status, monotherapy or combined therapy, and blood or urine culture results were all recorded and compared between LR and HR groups. Ethical approval was obtained from Local Ethics Committee. Informed consent was taken from all patients before the initiation of treatment. All participants completed the study.

2.2. Sample collection

Blood ADM samples from each patient were obtained at 0 (A1), 24 (A2), and 48 (A3) hours and on the 7th day of treatment (A7). Samples for the human adrenomedullin (hADM) assay were collected with disodium ethylenediamine tetraacetate (Na21 EDTA; 1 mg/ml) and aprotinin (Trasylol; Bayer, Leverkusen, Germany; 500 kIU/ml), and samples for other assays were collected with sterile heparin. All samples were cooled on ice. Plasma was separated by centrifugation at 3000 rpm for 10 min at 4 °C and stored at −80 °C until assayed.

2.3. Radioimmunoassay for hADM

Human adrenomedullin (hADM) was measured by an enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's protocol (Hangzhou Eastbiofarm Co. Ltd., Hangzhou, China). Intra-assay coefficient of variation (CV) of the ADM assay was <10% while inter-assay CV was <12%. The minimum detectable concentration for ADM was 2.52 ng/L. Measurements were carried out using a microtiter plate reader (Bio-Tek Synergy HT, Biotek Instruments Inc., Winooski, VT, USA). All the samples were measured in duplicate.

2.4. Statistical analysis

Statistical analyses were performed using SPSS software, version 15. The Mann–Whitney U test was used to compare A1, A2, A3, and A7 ADM levels between LR and HR groups. The change in ADM by time was analyzed using repeated-measures analysis of variance. Greenhouse-Geisser correction was used when the sphericity assumption was violated. The correlation coefficients and significance were calculated using the Spearman test. The capacity of ADM values to predict the presence of a high-risk

Table 1
Demographic and laboratory features of subjects.

	Data	SD
Demographic features		
Tension arterial (mmHg)	100/60	±8.1/6.9
Temperature at admission (°C)	38.5	±0.4
Duration of fever (day)	2	±3.5
Duration of grade 4 neutropenia (day)	3.5	±4.4
Duration of grade 3 neutropenia (day)	4	±5.1
In-patient follow up time (day)	7	±2.8
Laboratory examination		
WBC ($\times 10^3/mm^3$)	0.40	±0.6
Hb (g/dl)	8.9	±1.5
Neutrophil ($\times 10^3/mm^3$)	0.1	±0.3
Plt ($\times 10^3/mm^3$)	55	±119.3
ESR (mm/h)	80	±38.4
CRP (mg/L)	47	±103.7
Adrenomedullin levels at different time periods		
A1	551	±420
A2	558	±419
A3	579	±364
A7	546	±314
Disease	**Number of patients**	**%**
PNET	2	14
Ewing sarcoma	3	21
Hodgkin lymphoma	2	14
Neuroblastoma	3	21
Non-Hodgkin lymphoma	2	14
Osteosarcoma	1	7
Ependymoma	1	7
Types of fever		
FUO	27	75
Culture positive	8	22.2
Clinically proven	1	2.8
Types of treatment		
Monotherapy	15	41.7
Combined therapy	21	58.3
Modification		
Yes	14	38.9
No	22	61.1
GCSF		
Yes	29	80.3
No	7	19.7

Abbreviations: WBC: white blood cell, Hb: hemoglobin, Plt: platelet, ANC: absolute neutrophil count, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein.