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CASE REPORT

# A Very Rare Cause of Bicytopenia; The Use of Vitex Acnu Castus

**ABSTRACT**

Vitex Agnu Castus dry extract BNO 1095 is used in many indications, mainly premenstrual syndrome. Nausea, headache, acne, etc. are the main side effects. The use of BNO 1095 was learned from the history of a 27-year-old female patient who was examined for bicytopenia etiology. Serological tests results were within normal limits and the bone marrow biopsy clonality result suggested that this might be related to non-neoplastic autoimmune processes. The response to methylprednisolone treatment was accepted as a finding supporting this result. Although there are many reasons in the etiology of bicytopenia, the use of herbal medicine should always be considered. This is the first case in the literature demostrating that this herbal medicine causes bicytopenia.

**Keywords:** Bicytopenia, casticin, vitex agnu castus

Medicinal wild plants have been used as valuable tools in the management of different diseases for centuries due to their ease of use and cost effectiveness compared to chemical drugs obtained by synthesis (1).

Vitex agnus castus L. (VAC) is a bush type plant found in the Mediterranean parts of Europe and Central Asia. There are many conditions or diseases in which VAC extract is traditionally used, including menstrual disorders (amenorrhea, dysmenorrhea), premenstrual syndrome (PMS), corpus luteum failure, hyperprolactinemia, infertility, acne, menopause and impaired lactation (2). The various compounds in the chemical content of VAC are vitexilactone, rolundifuran, ketosteroids, diterpenoids (vitexlactam, vitexilactone, viteagnusin I and rotundifuran), flavonoids (orientin, kaempferol, penduletin, luteolin, artemetin, vitexin and casticin) and iridoids (agnusid, agnusosid, agnucastosid A/B and aucubin) (1).

In the European Union herbal monograph, the posology commends that products containing VAC dry extracts are used for irregular menstruation, premenstrual syndrome and mastalgia at 4 to 20 mg/day. These dry extracts are standardized in the European Pharmacopoeia (EP) to contain not less than 0.01% casticin in the extract (3).

Casticin is a polymethylflavonide derived mainly from the Vitex species of the Verbenaceae family. This substance isolated from VAC leaves has potent anti-inflammatory and lipoxygenase inhibitory activity. The molecular mechanism of its anti-inflammatory action is the blockade of the NF-kβ, Akt and mitogen-activated protein kinase signaling pathway (4).

## CASE

A 27-year-old female with no known chronic disease presented hospital with the complaints of weakness. The laboratory test results revealed bicytopenia: Leukocyte: 920/µL, neutrophil: 100/µL, hemoglobin: 10.6 g/dL, MCV: 68 fL, platelet: 211.000/µL. The patient was hospitalized for further examination. There were no B symptoms. Drug and herbal substance use was questioned and the patient reported having used BNO 1095 (generic name Agnucaston), which is a preparation of the dry extract of Fructus acnu casti for accessory breast, for 3 months and mpst recently 1 month ago.

Anemia parameters were within normal limits: Vitamin B12:231 ng/L, folat: 4.8 ug/L, ferritin: 72 ug/L. A peripheral blood smear was taken and evaluated. Anisocytosis was determined in the red blood cell morphology , leukocyte count compatible with complete blood count, and no atypical cells were seen. Viral hepatitis markers, TORCH panel, brucella, ANA,

**Merih Reis Aras**[1]
**Murat Albayrak**[1]
**Fatma Yılmaz**[1]
**Senem Maral**[2]
**Pınar Tığlıoğlu**[3]
**Mesut Tığlıoğlu**[3]
**Hacer Berna Afacan Öztürk**[1]
**Ahmet Kürşad Güneş**[1]

[1]*Department of Hematology, Ankara Etlik City Hospital, Ankara, Türkiye*
[2]*Department of Hematology, İstanbul Bağcılar Medipol Mega University Hospital, İstanbul, Türkiye*
[3]*Department of Hematology, Gaziantep Dr. Ersin Arslan Training and Research Hospital, Gaziantep, Türkiye*

**Corresponding author:**
Merih Reis Aras
✉ merihreis@gmail.com

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**Table 1. Naranjo Advers drug reaction probability scale—items and score**

| To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score | Yes | No | Don't know | Score |
|---|---|---|---|---|
| Are there previous conclusion reports on this reaction? | +1 | 0 | 0 | 0 |
| Did the adverse event appear after the suspected drug was administered? | +2 | -1 | 0 | +2 |
| Did the adverse reaction improve when the drug was discontinued, or a specific antagonist was administered? | +1 | 0 | 0 | +1 |
| Did the adverse reaction reappear when the drug was readministered? | +2 | -1 | 0 | 0 |
| Are there alternative causes (other than the drug) that could on their own have caused the reaction? | -1 | +2 | 0 | +2 |
| Did the reaction reappear when a placebo was given? | -1 | +1 | 0 | 0 |
| Was the drug detected in the blood (or other fluids) in concentrations known to be toxic? | +1 | 0 | 0 | 0 |
| Was the reaction more severe when the dose was increased, or less severe when the dose was decreased? | +1 | 0 | 0 | 0 |
| Did the patient have a similar reaction to the same or similar drug in any previous exposure? | +1 | 0 | 0 | 0 |
| Was the adverse event confirmed by any objective evidence? | +1 | 0 | 0 | 0 |

➔ Naranjo Score 5
➔ Adverse drug reaction: Probable
Note: The Naranjo criteria classify the probability that an adverse event is related to drug therapy based on a list of weighted questions, which examinefactors such as the temporal association of drug administration and event occurrence, alternative causes for the event, drug levels, dose–response relationships and previous patient experience with the medication. The ADR is assigned to a probability category from the total score as follows:
definite if the overall score is 9 or greater, probable for a score of 5–8, possible for 1–4 and doubtful if the score is 0. The Naranjo criteria do not take into account drug–drug interactions. Drugs are evaluated individually for causality, and points are deducted if another factor may have resulted in theadverse event, thereby weakening the causal association.

Anti-Ds DNA and SARS-COV2 PCR test were performed, and all were negative.

In the investigation of the etiology, ultrasound imaging showed a large number of cervical, axillary and inguinal lymph nodes, the largest of which were in the left axilla. This was a reactive lymph node in 20x6.7 mm size with an open hilum. Fine needle aspiration biopsy was performed on the right cervical lymph node, and it was reported as benign cytology.

Bone marrow aspiration and biopsy were performed. Flow cytometry was studied from the aspiration material. In the bone marrow aspiration evaluation; "normocellular bone marrow, megakaryocytes were found to be sufficient in number. Erythroid serial rate was increased (40%) and approximately 30% small, mature, narrow cytoplasmed atypical lymphoid cell infiltration was observed". The flow cytometry result was reported as: "Significant lymphocytosis and granulocytopenia, CD4 / CD8 ratio impaired in increased number of T lymphocytes [ratio 0.45, (reference range 1.3-3.6)]".

The bone marrow biopsy pathology was reported as "normocellular bone marrow showing increased CD3 (+) mature T cells, an increase in interstitial pattern containing interstitial multiple lymphoid aggregates" Considering possible lymphoproliferative or immunological processes, treatment iniated of 60 mg/day methylprednisolone.

The result of the clonality studied from the bone marrow biopsy were reported as; "Molecular findings supporting clonal T cell increase among polyclonal T cells are considered features supporting autoimmune neutropenia. Immunophenotypic and molecular findings observed in the bone marrow primarily suggest that the increase in clonal cytotoxic T cells on a polyclonal basis may be associated with non-neoplastic autoimmune processes".

As a result of bone marrow clonality, the methylprednisolone dose was reduced and then discontinued. The patient remains under follow-up and the hemogram parameters are completely normal.

## DISCUSSION

Over the last 50 years VAC has been used especially for the treatment of premenstrual syndrome and prevention of premenstrual mastalgia (5).

In a systemic review by Danielle et al. on the side effects of VAC treatment; the most commonly seen side effects were reported to be nausea, headache, gastrointestinal disturbances (nausea, vomiting, pressure sensation in the epigastric region, etc.), menstrual disorders, acne, itching and erythematous rash and these were seen to often be reversible (2).

Casticin is a potent immunomodulator and cytotoxic compound for which chemiluminescence, chemotaxis, T cell proliferation and cytotoxic activity have been tested in vitro. There has been reported to be a significant dose-dependent inhibitory effect on monocyte oxidative burst (6).

Casticin; decreases neutrophil, macrophage, and lymphocyte counts, proinflammatory cytokine and chemokine levels. It also significantly reduces the thickness of the epithelium and its infiltration by inflammatory cells (4).

Röhl et al., (7) showed that VAC dry extract BNO 1095 targets uterine myometrial tissue and inflammatory signaling molecules asso-

ciated with migratory / inflammatory cells. The same study also reported that BNO 1095 has a promising anti-inflammatory effect in in-vitro conditions through the stong inhibition of 5-lipoxygenase activity and leukotyrene production and reduction of the production of inflammatory cytokines and reactive oxygen derivatives.

The patient presented in the paper had used fructus agnu casti extract and the result of the bone marrow biopsy clonality suggested that it may be related to autoimmune processes. The hemogram parameters returned to normal in a short time after discontinuation of the extract, suggesting that this event was related to this extract.

The assessment of causality between fructus agnu casti extract and bicytopenia using the Naranjo nomogram questionnaire yielded a score of 5, indicating that the side effect probably caused which means side-effect is probably caused by the fructus agnu casti extract (Table 1) (8).

The aim of presenting this case was to emphasize that patients who are investigated for cytopenia should be questioned about the use of herbal substances in addition to medications and the possible side-effects of herbal products should be considered. This case also provides an example of the effectiveness of steroid therapy in the treatment of cytopenias triggered by autoimmunity.

There are no previous cases in the literature that this preparation causes bicytopenia. So this case report can be considered important due to its rarity and clinical significance.

**Informed Consent:** Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

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