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Letter to the Editor

Thrombocytopenia associated with high levels of inhibin. A case study

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Inhibins are glycoprotein hormones that belong to the Transforming Growing Factor β superfamily [1]. They exist under two major types, inhibin A (αβA) and inhibin B (αβB), depending on which isoform of the β-subunit, βA or βB, is added to the constant alpha subunit [2]. In females, both are produced by the granulosa cells of the ovary [1]. By negative feedback on the pituitary-gonadal axis, they downregulate the synthesis of Follicle Stimulating Hormone (FSH) which has a primary role in the growth and recruitment of ovarian follicles [3]. Inhibins also have described roles in bone metabolism, adrenal function, retinal development, pregnancy, organogenesis and hematopoiesis [1].

A 40-year-old woman presented to our emergency room with menometrorrhagia, pelvic pain for six months, generalized weakness and pallor. Physical examination showed a large tender mass in the lower abdomen. Computed Tomography showed a rounded heterogeneous mass of 27 × 32 × 20 cm arising from the uterus. Transvaginal ultrasound showed that the mass arose from the right adnexa. She had no other signs of bleeding.

She had a normochromic normocytic anemia of 7 g/dl (Reference: 11.1–14.6 g/dl) with a low total reticulocyte count response by reticulocyte index, normal iron level at 145 μcg/dl (Reference: 37–170 μcg/dl), ferritin levels at 111 ng/ml (Reference: 13–150 ng/ml) and total iron-binding capacity at 372 μcg/dl (Reference: 265–347 μcg/dl).

Her initial platelet count was 40×10^3 μcl (Reference: 140–400 × 10^3 μcL) but fell to 16 within 24 h. Her white blood cells of 3.8×10^3 μcL (Reference: 4–10.5 × 10^3 μcL) without neutropenia. Peripheral smear showed rare teardrop cells, no hypersegmented neutrophils, severe thrombocytopenia, no spherocytes, no schistocytes or other findings suspicious of hemolysis or microangiopathy.

Hematologic workup included levels of Vitamin B12 at 232 pg/ml (Reference: 211–946 pg/ml), folate level at 5.9 ng/mL (Reference: 7.3–26.1 ng/ml) with methylmalonic acid levels of 113 nmol/L (Reference: 87–318 nmol/L) excluding vitamin B12 borderline low level as the cause. Additional workup included normal copper and zinc levels, negative serologies for HIV, viral hepatitis and parvovirus. There was no evidence of disseminated intravascular coagulation with normal coagulation times and fibrinogen although fibrin degradation fragments were elevated at 838 ng/dl (Reference: 0–230 ng/dl). Hemolysis workup included elevated lactate dehydrogenase (LDH) at 1665 units/L (Reference: 313–618 units/L), low haptoglobin at < 10 mg/dl (Reference: 30–200 mg/dl), without signs of hemolysis and negative antiglobulin tests.

Over hospital course, platelets fluctuated in between 8 and 59 × 10^3 μcL, responding adequately to three pooled platelet transfusions. Her symptomatic anemia resolved after transfusion of three units of packed red blood cells and hemoglobin remained stable at 10.7 g/dl. Bone marrow aspirate and biopsy showed a hypocellular bone marrow with erythroid hypoplasia and mildly dyspoietic megakaryocytes. Bone marrow also showed a low degree of fibrosis and mild stromal edema with increased iron stores. No immunophenotypically abnormal lymphocyte populations were identified by flow cytometry and karyotype was normal.

Gynecology workup included levels of Ca125 at 13 units/ml (Reference: 0–35 units/ml) and alpha fetoprotein (AFP) at 0.7 ng/ml (Reference: < 8.7). Results of Inhibin A and B levels came back over a week after presentation with Inhibin B at > 1300 pg/ml (Reference for premenopausal female: < 153 pg/ml), Inhibin A at 2636 pg/ml (Reference for premenopausal female < 93 pg/ml).

Once medically stabilized she underwent a total hysterectomy, bilateral salpingo-oophorectomy and left pelvic lymph node sampling. Pathology revealed a stage IA granulosa cell tumor of 43 × 23 × 18 cm in size of the right ovary.

In the days immediately following surgery, both inhibin A and B levels dropped rapidly. She was discharged on a postoperative day 4 without complications. Over the next 2 months, her inhibin B and A dropped to undetectable levels and her platelets normalized (Fig. 1).

To our knowledge this report represents the first clinical documentation of pancytopenia with high inhibin levels. Although this potential relationship has been established in-vitro [1,4,5], it has never been reported clinically.

Broxmeyer et al. [5], showed in vitro the effects of recombinant human inhibin A in suppressing the granulocyte, erythrocyte, monocyte, and megakaryocyte colony-formation units (CFU-GEMM) in the presence of erythropoietin and in a dose direct manner. Also showed that on exclusion of monocytes and T-lymphocytes from culture, the suppressing effect seemed to be lost suggesting that the effect is induced by inhibin on progenitor cells is indirect. Hangoc et al. [4] showed a

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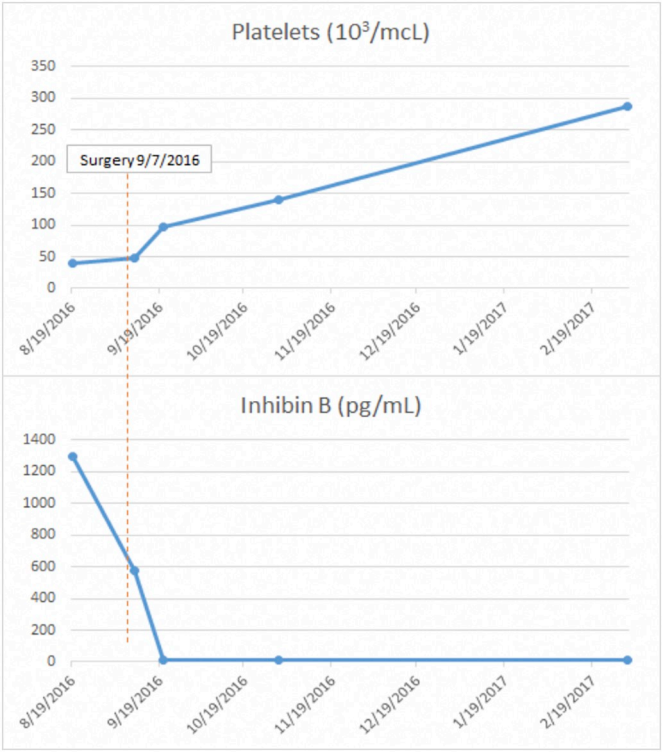

Fig. 1. Platelet and inhibin B levels before and after surgery.

reduction in the number of CFU-GEMM after treating mice with intravenous recombinant human inhibin.

Two previous reports have presented cases of pancytopenia in the setting of a GTC, although without documentation of inhibin levels. Napoli and Wallach [6] presented the case of a GCT with thrombocytopenia, anemia, elevated LDH and a hypocellular bone marrow that resolved after tumor resection. A second case by Mercolini et al. [7] reportedthrombocytopenia and anemia in a pediatric patient with an AFP-producing GCT. In the latter, bone marrow was normocellular and anemia and thrombocytopenia resolved on final tumor resection.

Despite the three hematopoietic lines diminished in peripheral blood and on bone marrow samples, platelet counts demonstrated a stronger inversely clinical correlation with the inhibin levels. High levels of LDH in the absence of hemolysis may be secondary to the tumor or ineffective hematopoiesis but we cannot explain low levels of haptoglobin in the absence of liver disease or hemolysis. Haptoglobin was obtained one time and there are no consecutive values were followed.

Granulosa cell tumors account for 5% of all ovarian tumors and inhibin B is the predominant form expressed in GCT is currently the preferred marker for differential diagnosis and follow up of GCT [8]. A retrospective cohort intending to validate biologic markers for differential diagnosis and follow up of GCT showed that Inhibin B was the most specific marker but with median level of 211.5 pg/dl (Reference levels in premenopausal woman < 200 pg/dl). [8] They reported one case with extremely high levels on inhibin, although no association with pancytopenia was reported. Our case presents as an unusual elevation of Inhibin B considering the latter.

Given the rarity of this tumor and unusual presentation, it is possible that suppressive marrow effects occur with exceedingly high levels of inhibin. It is reasonable to consider possible surgical intervention in cytopenic patients with elevated inhibin levels.

Author contributions

NG had the overall clinical responsibility, performed chart review and wrote initial draft and final manuscript. RC participated in critical writing of final manuscript, interview the patient and wrote initial draft of the manuscript. AT participated in critical writing of final manuscript and editing. TH provided expert opinion and final review of manuscript.

Conflict of interest statement

The authors state that they are no conflict of interests regarding the publication of this article.

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Nicolas Gallastegui[a,*], Ryan M. Coe[b,1], Alfredo Torres[a], Thomas J. Harrington[a,c]
[a] *Division of Hematology, Department of Medicine, University of Miami Leonard M. Miller School of Medicine/Sylvester Comprehensive Cancer Center, United States of America*
[b] *Division of Medical Education, University of Miami Leonard M. Miller School of Medicine, United States of America*
[c] *Division of Pediatric Hematology, Oncology & Stem Cell Transplantation, Department of Pediatrics, Hemophilia Treatment Center, University of Miami Leonard M. Miller School of Medicine, United States of America*
E-mail address: n.gallastegui@med.miami.edu (N. Gallastegui).

* Corresponding author at: Department of Medicine, Division of Hematology, University of Miami Leonard M. Miller School of Medicine/Sylvester Comprehensive Cancer Center, 1475 NW 12th Ave, Hope Building, Room 335, Miami, FL 33136, United States of America.
[1] **Current affiliation**: Department of Medicine. Oregon Health & Science University.