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Unforeseen encounter of acquired hemophilia A in a preoperative case of periampullary carcinoma: A case report

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ABSTRACT

INTRODUCTION: Acquired hemophilia A (AHA) is a rare disorder characterized by development of antibodies against factor VIII, which can present as paraneoplastic syndrome in various malignancies like periampullary cancer, cancer of lung, prostate, gastrointestinal stromal tumour and non malignant cases like pregnancy, autoimmune disease and medication.
CASE PRESENTATION: We report a case of elderly man presented with paraneoplastic AHA in periampullary carcinoma in preoperative period which was diagnose by mixing study and inhibitor assay and managed with bypass agents like recombinant factor VII, FEIBA and immunosuppresion to eliminate inhibitor with help of steroid, cyclophosphamide and emicizumab. Patient underwent Whipple's pancreaticoduodenectomy after which coagulation study became normal in immediate postoperative period. Patient was discharged and followed up with chemotherapy.
CLINICAL DISCUSSION: Periampullary carcinoma presenting as AHA is rare and rarer in pre-operative settings. The usual mode of presentation is bleeding after biopsy and from minor surgical scars. The pathogenesis is yet to be delineated. It is managed by factor VIII administration and immunosuppressive therapy.
CONCLUSION: High index suspicion should be there to diagnose AHA as a paraneoplastic manifestation and elective surgery should be delayed till normalization of coagulation parameters.

1. Introduction

To identify the cause of recent onset bleeding in patient with any malignancy is quite challenging [1]. Disseminated intravascular coagulation and autoimmune thrombocytopenia are frequently encountered cause of malignancy associated bleeding. A rare cause of malignancy associated bleeding is inhibitory antibodies against coagulation factors [2]. Acquired hemophilia A (AHA) is rare but potentially life threatening bleeding disorder characterized by development of auto antibodies against factor VIII in cases of malignancy, autoimmune disorders, pregnancy and due to medications [3]. AHA presenting as paraneoplastic syndrome in lung, prostate, bladder, gastrointestinal and hematological malignancy had been described before in postoperative cases [4]. Only few cases of AHA associated with periampullary carcinoma had been reported in literature and mostly in postoperative period. We report our experience of a case AHA presenting as paraneoplastic syndrome in periampullary carcinoma during pre-operative period.

2. Case report

78 year old male, a known hypertensive since last 5 years was found to have intrahepatic biliary radical dilatation on ultrasound during routine health checkup. His LFT showed cholestatic pattern with elevated bilirubin (Total/Direct – 6.5/4.25). He was evaluated with CECT abdomen which showed dilated common hepatic duct, common bile duct (CBD) with an ill defined round hypodense lesion measuring (19 × 19) mm in head of pancreas infiltrating into distal CBD. He subsequently developed jaundice, ecchymotic patches (Fig. 1) over bilateral upper and lower limb along with bilateral lower limb edema. CT angiography abdomen done to assess the resectibility showed a nodular lesion at ampulla without any major vascular involvement (Fig. 2). MRI of lower limb showed diffuse subcutaneous and myofacial edema from gluteal area to proximal leg region. Upper GI endoscopy showed an ulcerated exophytic growth at ampulla (Fig. 3) and biopsy was suggestive of moderately differentiated adenocarcinoma. Post biopsy patient had persistent melena and fall in hemoglobin. On further evaluation, his aPTT was

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Fig. 1. Right upper limb showing subcutaneous bleeding.

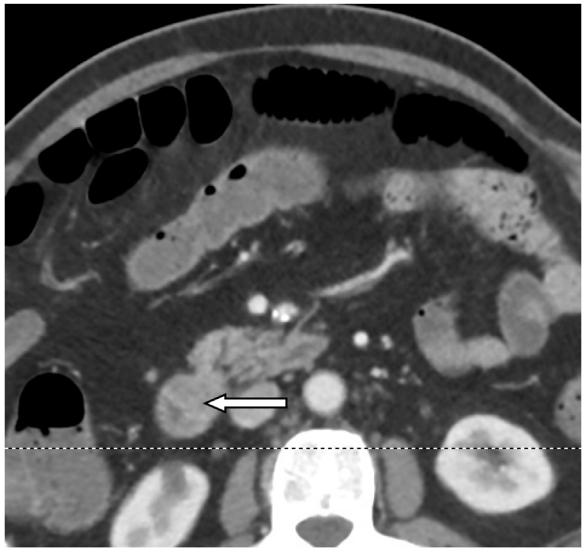

Fig. 2. Computed tomography showing periampullary lesion (White arrow).

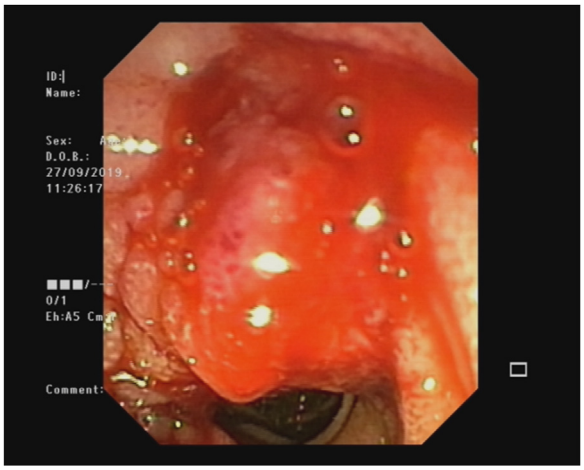

Fig. 3. Periampullary lesion in upper GI endoscopy.

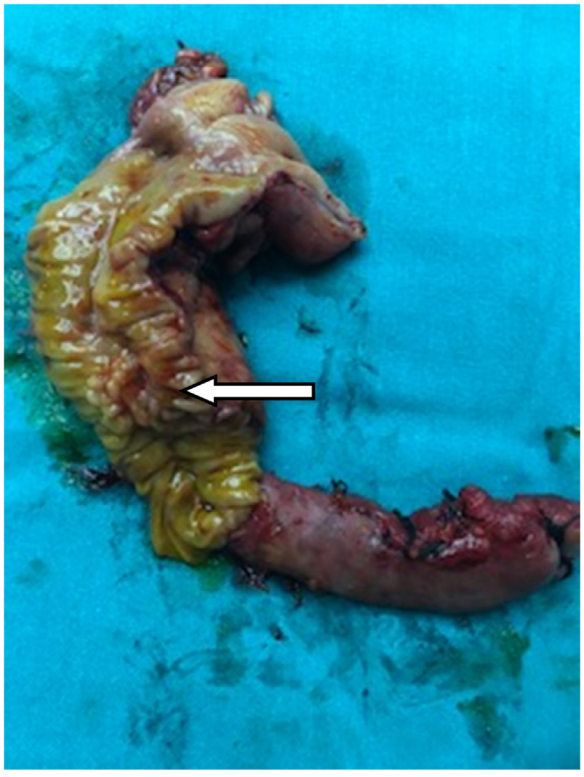

Fig. 4. Resected Whipple's specimen showing periampullary lesion (White arrow).

markedly elevated (105 s). The factor VIII assay revealed a value of 2.5% and mixing study revealed late onset inhibitor. Bethseda assay revealed factor VIII inhibitor titer of 34 BU/mL. A diagnosis of acquired hemophilia A (Factor VIII inhibitor with high titer) was made. There was no history of previous bleeding disorder, drug history, known genetic predisposing factors or any suggestive family history. He was then started on recombinant factor VII along with steroid and cyclophosphamide, but he remained transfusion dependent and melena persisted. The recombinant factor VII was changed to FEIBA (Factor Eight Inhibitor Bypass Activity) but there was no clinical improvement. In view of persistent transfusion dependency, patient was started on emicizumab. Post emicizumab, melena stopped and he became transfusion independent. Repeat aPTT was 32 s and ROTEM showed normal INTEM/EXTEM graphs suggestive of normal in vivo coagulation. He underwent Whipple's pancreaticoduodenectomy, by senior consultant gastrointestinal surgery, who regularly performs such surgeries; with an intraoperative blood loss of 100 mL. Postoperative coagulation parameter remain in normal limit with disappearance of echhymotic patches and limb swellings, without any need of further intervention. He was discharged on post operative day 11 with an uneventful post op recovery. The biopsy showed moderately differentiated adenocarcinoma with lymphovascular, perineural invasion and received chemotherapy (Gemcitabine + Cisplatin) and is doing well in subsequent follow up (Figs. 4 and 5).

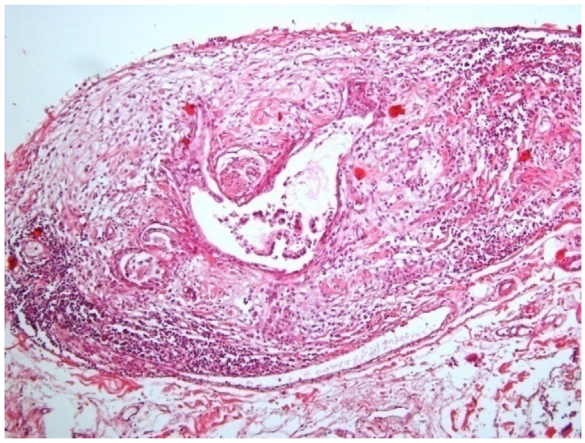

Fig. 5. Histopathology showing adenocarcinoma arising from duodenum.

3. Discussion

Para – neoplastic syndrome is a constellation of symptoms or laboratory abnormalities not induced by metastatic tumor or any local cause. This may be due to immunological reactions or any biological substance produced by the body in response to tumor [5]. The prevalence of paraneoplastic syndrome in cancer patient is 8% which is more likely to increase because of better diagnostic method and increase in survival. The most commonly associated malignancies include small cell lung cancer, breast cancer, gynecologic tumors, and hematologic malignancies [6].

Autoimmune thrombocytopenia, factor VIII inhibitor, autoimmune hemolytic anemia, antiphospholipid antibody are usual paraneoplastic hematological manifestation of malignancy [5,7]. AHA is a rare clinical condition which presents as sudden, severe and potentially life threatening hemorrhages. It has an incidence of 0.2–1.48 per 100,000 population. The postulated theory behind AHA is development of immunue tolerance mechanism which is characterized by the synthesis of lgG oligoclonal or restricted polyclonal antibodies, that are targeted against and neutralize the coagulation function of factor VIII: C. It is considered as autoimmune paraneoplastic condition due to synchronous or metachronous development with primary malignancy [8]. In many solid tumor antibody against factor VIII can be seen which may considered as paraneoplastic syndrome [3]. Case report of solid organ malignancy with acquired hemophilia had been reported previously in gastrointestinal stromal tumor, duodenal and pancreatic cancer [8]. Prevalence of paraneoplastic FVIII inhibitors is 11.8% according to European Acquired Haemophilia Registry (EACH2) out of which 67.8% associated with solid tumors and 32.2% in hematological malignancies [4]. Sometimes it disappears after surgery with removal of cause as happened in our case [9].

Mavroeidis et al. and Geethakumari et al. had reported paraneoplastic hemophilia associated with pancreatic cancer [10,11]. We report our experience of another case of paraneoplastic hemophilia associated with periampullary cancer in an elderly patient in preoperative period after thorough investigation and management.

Usually AHA is seen in post operative period as seen in literature review by S. Reitter et al. in 4 cases of pancreatic cancer [4]. Similarly Mavroeidis et al. reported AHA in postoperative case carcinoma of ampulla of vater after two month of surgery which was attributed to peritoneal metastatic disease which was also confirmed by Geethakumari et al. adenocarcinoma of pancreas [10,11]. None of the cases reported in preoperative period as per our knowledge.

According to Sallah et al. immune dysfunction caused by abnormal T cell response to tumor antigen or abnormal interaction of T and B cell resulted in development of inhibitor antibodies against factor VIII [12]. However it is established for hematolological malignancy. The mechanism regarding developement of autoantibodies against factor VIII in solid tumor is yet to be established. However it is thought to be due to resemblance of factor VIII with tumor antigen and subsequent autoimmune respose [13]. S. Reitter et al. also supported this theory [4].

Cases of anti-FVIII autoantibody patients bleeding into skin, muscle, mucosal surface of nasal, digestive tract, genitourinary tract in 80% of cases [3,14]. Fig. 1 shows typical presentation in our case. Bleeding into body cavities like intracranial, retroperitoneal, retropharyngeal also seen but bleeding into joint seldom occurs which is a characteristic of congenital hemophilia. Laboratory investigation like full blood count, platelet count and coagulation profile should be done. Usually a prolonged aPTT with normal PT is found in AHA [15]. Factor VIII inhibitor should be differentiated from coagulation factor deficiency (FVIII, IX, XI or XII). Lupus anticoagulant can confuse with inhibitor but it is normal if inhibitor against factor VIII is elevated. Mixing test in which patients plasma is mixed to pooled plasma at 1:1 ratio will differentiate between a inhibitor and factor deficiency. Bethesda assay, anti-porcine inhibitor titer, anti FVIII immunosorbent assay can be performed to measure inhibitor [15].

Untreated cases may result in worsening of condition in patient with intramuscular, mucocutaneous bleeding. Providing immediate hemostatic therapy and monitoring its outcome by means of improvement in anemia and clinical condition is required [16]. Control of bleeding is the first priority followed by elimination of inhibitor and finding of underlying cause. Bypassing agent like recombinant factor VIIa and activated prothrombin complex concentrate (APCC) containing factor II, VII, IX, X is beneficial for life threatening bleeding. Factor VIII administration can help in neutralizing inhibitor but the quantity and half-life is difficult to qualify along with it monitoring of hemostatic function should be done with aPTT and FVIII:C [16]. If inhibitor titer is low, desmopressin and factor VIII replacement can be given. Desmopressin increases FVIII:C by release of factor VIII and Von Willebrand factor but less effective on repeated administration. If possible, invasive procedure to be avoided otherwise replacement therapy before and after the procedure to be given [10].

For normalization of hemostatic function, inhibitor immunosupression is the main modality [17]. Combination therapy of high dose FVIII administration, immunoadsorption and immunosupression reported to be effective for AHA treatment [18]. Steroid alone or in combination with cyclophosphamide and rituximab are used in most of centres [9]. Other immunosuppressive agent like azathioprine, cyclosporine, mercaptopurine and vincristine can be used [15]. Protein A adsorption column and plasmapheresis can remove inhibitor for short-time in case of active severe bleeding [19]. Sallah et al. reviewed 41 patient of AHA associated with malignancy and found 70% complete response with 22% complete remission among responder after treatment of cancer [3]. M. Napolitano et al. also reported complete response in 62.1% [20].

4. Conclusion

AHA as paraneoplastic manifestation of periampullary carcinoma is itself a rare condition and to present in pre operative setting makes our case a unique one. Clinician should have a low threshold and high index of suspicion while evaluating a pre operative patient with recent onset bleeding. Multidisciplinary involvement is a definite while managing such patients. Elective surgery should be postponed till correction of coagulation parameters. There is a need of large sample study of paraneoplastic AHA in periampullary carcinoma to establishment its etiology and management protocol.

The work has been reported in line with the SCARE 2020 criteria [21].

Declaration of Competing Interest

The authors report no declarations of interest.

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None.

Ethical approval

Taken.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Suvendu Sekhar Jena – Data collection and analysis. Writing paper.

Dibyasingh Meher – Writing the paper and data interpretation.

Neha Dhankar – Study concept and design.

Registration of research studies

Not applicable.

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Suvendu Sekhar Jena.

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References

[1] M.A. Escobar, Bleeding in the patient with a malignancy: is it an acquired factor VIII inhibitor? Cancer 118 (2) (2012) 312–320.
[2] P.M. Mannucci, Overview of bleeding in cancer patients, Pathophysiol. Haemos. Thromb. 33 (2003) 44–45.
[3] M. Franchini, G. Gandini, T. Di Paolantonio, G. Mariani, Acquired hemophilia A: a concise review, Am. J. Hematol. 80 (1) (2005) 55–63.
[4] S. Reitter, P. Knoebl, I. Pabinger, K. Lechner, Postoperative paraneoplastic factor VIII auto-antibodies in patients with solid tumours, Haemophilia 17 (5) (2011) 889–894.
[5] A. Hariz, M.S. Hamdi, I. Boukhris, E. Cherif, Autoimmune haemolytic anaemia in pancreatic adenocarcinoma: a potential paraneoplastic presentation, BMJ Case Rep. 12 (7) (2019), e229807.
[6] L.C. Pelosof, D.E. Gerber, Paraneoplastic syndromes: an approach to diagnosis and treatment, Mayo Clin. Proc. 85 (9) (2010) 838–854.
[7] H. Yu, R. Fu, H. Wang, H. Liu, Z. Shao, Paraneoplastic Evans syndrome in a patient with adenocarcinoma of the lung: a case report, Thorac. Cancer 8 (January (1)) (2017) 57–60.
[8] I.S. Nenova, M.Y. Valcheva, E.A. Beleva, D.Y. Tumbeva, M.P. Yaneva, E.L. Rancheva, et al., Autoimmune phenomena in patients with solid tumors, Folia Med. (Plovdiv) 58 (3) (2016) 195–199.
[9] A. Arain, I.N. Muhsen, M. Abdelrahim, Acquired haemophilia as a paraneoplastic manifestation of pancreatic cancer, Ecancermedicalscience 14 (2020) 1053.
[10] L. Mavroeidis, A. Vassou, G. Zarkavelis, A. Papadaki, I. Mouzaki, P. Ntellas, et al., Acquired hemophilia in an elderly patient with carcinoma of the ampulla of vater, Case Rep. Oncol. 13 (2020) 1–6.
[11] P.R. Geethakumari, A. Sama, J.G. Caro, C.J. Yeo, S. Nagalla, "The immune conundrum": acquired hemophilia a, immune thrombocytopenia, and neutropenia in a patient with pancreatic cancer, Case Rep. Pancreat. Cancer 2 (1) (2016) 14–18.
[12] S. Sallah, N.P. Nguyen, J.M. Abdallah, L.R. Hanrahan, Acquired hemophilia in patients with hematologic malignancies, Arch. Pathol. Lab. Med. 124 (2000) 730–734.
[13] B.T. Laselle, L.N. Boggio, M.G. Blum, Presentation and management of a stage Ia lung cancer patient with a paraneoplastic factor VIII inhibitor, Ann. Thorac. Surg. 81 (1) (2006) 362–364.
[14] M. Franchini, A. Tagliaferri, P.M. Mannucci, The management of hemophilia in elderly patients, Clin. Interv. Aging 2 (2007) 361–368.
[15] P. Collins, F. Baudo, A. Huth-Kühne, J. Ingerslev, C. Kessler, M. Mingot, et al., Consensus recommendations for the diagnosis and treatment of acquired hemophilia A, BMC Res. Notes 3 (2010) 161, http://dx.doi.org/10.1186/1756-0500-3-161.
[16] Yoshihiko Sakurai, Tomohiro Takeda, Acquired hemophilia a: a frequently overlooked autoimmune hemorrhagic disorder, J. Immunol. Res. (2014) 10, Article ID 320674.
[17] M. Greaves, H. Cohen, S.J. MacHin, I. Mackie, Guidelines on the investigation and management of the antiphospholipid syndrome, Br. J. Haematol. 109 (4) (2000) 704–715.
[18] H. Zeitler, G. Ulrich-Merzenich, L. Hess, E. Konsek, C. Unkrig, P. Walger, et al., Treatment of acquired hemophilia by the Bonn-Malmo Protocol: documentation of an in vivo immunomodulating concept, Blood 105 (6) (2005) 2287–2293.
[19] M. Franchini, Acquired hemophilia A, Hematology 11 (2) (2006) 119–125.
[20] M. Napolitano, S. Siragusa, S. Mancuso, C.M. Kessler, Acquired haemophilia in cancer: a systematic and critical literature review, Haemophilia 24 (1) (2018) 43–56.
[21] R.A. Agha, T. Franchi, C. Sohrabi, G. Mathew, for the SCARE Group, The SCARE 2020 guideline: updating consensus Surgical CAse REport (SCARE) guidelines, Int. J. Surg. 84 (2020) 226–230.