

Congenital Protein C Deficiency in Small Infant

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Congenital protein C deficiency is a rare inherited disorder, we are presenting a case manifested by sudden gangrenous lesion affecting his thigh, initial diagnosis was erythema gangrenosa. further work-up showed positive family history of 6 neonatal deaths with similar undiagnosed condition, and very low level of protein c. Patient improved after receiving anticoagulant and his life was saved. This is the first reported case in our community with congenital protein c deficiency.

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Hypercoagulable (Prethrombotic) state include a group of inherited and acquired disorders that cause a pathological thrombotic tendency or risk of thrombosis. Hypercoagulable State (HS) could be primary or secondary, Primary HS associated with life long predisposition to thrombosis and could be quantitative or qualitative. Secondary HS is a diverse group of mostly acquired conditions that cause a thrombotic tendency by complex and often multi-factorial mechanisms.

Congenital protein C deficiency (CPCD) is one variety of primary hypercoagulable state first described by Griffin and coworkers in 1981¹. CPCD leads to unregulated fibrin generation because of impaired inactivation of factor VIIIa and Va. and absence of its fibrinolytic activity^{2,3}. CPCD is rarely diagnosed in small infant and usually mistaken as disseminated intravascular coagulopathy (DIC) secondary to sepsis. We are presenting a case of small infant with CPCD for the first time in this part of the world.

THE CASE

Two and half month old female Kuwaiti patient admitted to the hospital with history of black lesion on her right thigh noticed by her mother just few hours before admission. Mother gave history of Diphtheria, Pertusis, Tetanus vaccination few days earlier in the same site of lesion followed by small swelling which increased in size after doing massage and hot compression and became indurated. No history of fever, vomiting or change in feeding pattern. No history of other skin lesion or rash, joint swelling, bleeding, convulsion cyanosis or respiratory distress.

The mother gave history of swelling in the left leg at 4 weeks of age diagnosed as cellulitis, treated with antibiotics for 2 weeks where she improved. She is the product of full term uneventful pregnancy and spontaneous vaginal delivery with birth weight of 3.25 kg. She is the first baby for her first-degree cousin parents. There is history of 6 neonatal deaths on the father's side with similar undiagnosed illness.

Healthy looking, playful, no pallor, no jaundice, no cyanosis, no dysmorphic features. She was afebrile, and with normal vital signs. There was black lesion in the antero-lateral aspect of her right thigh sized 8x8 cm, indurated, firm, hot, tender and surrounded with erythema (figure 1).

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Figure 1: The lesion on the right thigh on admission showing indurated extensive necrotic, gangrenous lesion surrounded by erythema.

There was no other skin lesion, no palpable lymph nodes or organomegaly. Other systems were normal.

The patient was admitted with the provisional diagnosis of Ecthyma gangrenosum, Coagulopathy and started empirically on ceftazidim, amikacin. Early investigation showed no growth in the blood culture (see table 1).

Table 1. Investigation

	WBCs*	Hgb*	Platelets*	ESR*	PT*	PTT*	FDP*
Day 0	8920 /cum m	10 gm /dl	284,000 /cum m	5	15 sec (Normal)	52 sec (Prolonged)	>4000 (High)
Day 4					Normal	Normal	>2000

WBCs: White Blood Cells
 Hgb: Hemoglobin
 ESR: Erythrocyte Sedimentation Rate
 PT: Prothrombin time
 PTT: Patrial Thromboplastin Time
 FDP: Fibrin Degradation Products.

Accordingly daily fresh frozen plasma was added to the regimen. On day 4, Patrial Thromboplastin Time (PTT) became normal, but Fibrine Degredation Product (FDP) remained high (2000); and Fresh Frozed Plazma (FFP) was discontinued. On day 8, suddenly, the patient developed another similar lesion in the anterior-lateral aspect of the left thigh sized 5x5 cm with induration. Needle aspirate from the new lesion for gram stain and culture were negative. Patient was labeled as a hypercoagulable status and blood sample was taken for coagulation factor, antithrombin III, Protein S and Protein C estimation. The coagulation factors VII, VIII, IX, XI, XII were in the lower limit of normal even on mixing test with normal plasma. Sample was sent for Anti-phospholipids Ab and Anti-cardiolipin Ab to role out lupus inhibitors. The result was negative. Protein C level was very low , protein S was normal (Table 2). Final Diagnosis: Congenital Protein C deficiency.

Table 2. Result of protein C and protein S assay

Name of the test	Result	Normal value
Protein C, Immunologic assay	<0.01 u/ml	0.64 -1.13 u/ml
Protein C, Functional assay	<0.01 u/ml	0.5 - 1.24 u/ml
Protein S Total	1 u/ml	0.56 - 1.19 u/ml
Protein S Free	0.85 u/ml	0.51 - 0.91 u/ml

The patient started on Warfarin 2 mg once daily aiming to keep International Normalization Ratio of 2-3 then sent home with advice for follow up after 4 weeks. She was found well with no new

lesion and her International Normalization Ratio was within acceptable level. The first lesion healed by secondary intention and the second lesion healed without scar.

After 3 months of treatment, while she was not in acute consumption state, protein C was repeated and showed same very low limit. The diagnosis of CPCD was confirmed.

DISCUSSION

Protein C is vitamin K-dependant glycoprotein that circulates in plasma as an inactive zymogene⁴. Thrombin is able to rapidly activate protein C when bound to thrombomodulin, an integral plasma membrane receptor that is present on vascular endothelial cells⁵. Two types of protein C deficiency are known: Type I Proportionate quantitative decrease in protein C (PC) antigen and activity; Type II: Qualitative defect in PC with disproportionately reduced PC relative to antigen. CPCD is inherited as autosomal dominant trait with variable expression⁶. Autosomal recessive trait had also been suggested⁷. More than 160 mutations are known to cause CPCD⁶. Affected individuals are heterozygotes (mostly) or homozygotes. The disease is present with 1:250 (antigenic assay) – 1:500 (functional assay). CPCD is found in 3-4% of patient with venous thromboembolism⁸⁻¹⁰. Most of the heterozygous are asymptomatic, and they need additional risk factors, acquired and/or genetic, to provoke thrombosis in heterozygous PCD patients⁸⁻¹⁰. Up to 20% of symptomatic CPCD patients also had activated protein C resistance⁸⁻¹⁰. Three clinical syndromes are associated with CPCD: Venous thromboembolism in heterozygous adult⁸⁻¹⁰, Neonatal purpura fulminans in homozygous newborns⁸⁻¹⁰ and warfarin-induced skin necrosis in certain heterozygous adult⁷. The first presentation of the patient was in the neonatal period with small thrombotic lesion, misdiagnosed as cellulitis and healed spontaneously but the diagnosis was missed. The second was at the age of 2 months with rapidly progressing gangrenous lesion in the right thigh followed shortly by similar lesion in the left thigh. The diagnosis was revised in based on the previous patient's history and the family history of 6 neonatal deaths due to similar condition which suggest genetic disorder; rapidly progressive lesion in a well looking baby not coinciding with the usual pattern of infection, negative cultures and persistent high level of Fibrin Degradation Product. Further study for genetic form of coagulopathy, revealed difficulty in interpretation of his initial low level of PC, although, it was done after 4 days of stopping Fresh Frozed Plazma. PC level was repeated after several months while the patient was not in acute consumption state, the result showed persistent low level which makes the diagnosis of CPCD is most likely.

Screening of both parents and other family members is indicated but it was not done because of financial difficulties.

As our patient was a symptomatic case of CPCD, anticoagulant (Warfarin) started aiming to keep International Normalization Ratio at 2-3 with a plan to continue warfarin for life¹¹. The patient was seen after several months and she was doing well. Protein C replacement therapy could not be given to the patient, as it was not available.

CONCLUSION

COPD should be one of the differential diagnoses of rapidly progressing gangrenous lesion especially in healthy looking baby.

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