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Late-onset pubic-phallic idiopathic edema in premature recovering infants

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Abstract:
Objective: Several cases of isolated localized edema of the genital area in extremely low birth weight (ELBW) infants within the last 5 years prompted a search for possible explanations and a search of the literature.
Study design: A retrospective chart review of all cases of localized genital area edema in our 16-bed community level-3 neonatal intensive care unit (NICU) between January 2007 and December 2017.
Results: A total of six patients with localized edema of the genital area were found. Among the six cases, five provided descriptions of time of onset. Only one case had a plausible etiology [inguinal hernia (IH)].
Conclusions: To our knowledge, this entity is not well described in the literature. Etiologies are speculative. Prolonged observation in the NICU by virtue of ELBW-status suggests that there are no detrimental effects, the condition does not appear to preclude discharge and cautious expectant management and reassurance are therefore in order.

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Introduction

Edema occurs in situations of increased capillary permeability (such as in inflammation), elevated capillary-hydrostatic pressure (such as in venous- or lymphatic obstruction), in lymphatic malformations or with decreased capillary-oncotic pressure (such as in abnormal loss of or decreased synthesis of plasma proteins as seen in renal and liver disease.) "Pitting" refers to the ability to mechanically remove the excess interstitial fluid by external compression.

"Organized" or "non-pitting" or "brawny" edema occurs when the leaked plasma proteins (especially fibrinogen) coagulate within the interstitial space and entraps the fluid in the form of a gel [1], [2].

Generalized edema is common in critically ill neonates and etiologies include, for example, a systemic inflammatory response, lymphatic malformations, hydrops, liver and renal failure. Dependent edema of eyelids, scrotum and lower legs are frequently seen in respiratory distress syndrome (RDS).

Table 1 illustrates different combinations of terms for describing edema.

Table 1: Combinations used in describing edema.

By mechanism	Lymphatic edema	Venous (hydrostatic) edema	Nutritional (oncotic) edema	Capillary leak (inflammatory) edema
By clinical appearance	Pitting edema		Non-pitting (brawny, organized, hard) edema	
By etiology	Primary edema – Lymphatic malformation		Secondary edema – Lymphatic obstruction	

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		– Lymphatic leak – Venous obstruction – Congestive heart failure – Renal failure – Liver failure – Malnutrition – Malabsorption – Inflammation (trauma, surgery, infection)
By influence of gravity	Dependent	Non-dependent
By extent	Generalized	Localized
By location	Genital, pubic, penile, peno-scrotal, facial, scalp, nuchal, pedal, etc.	

Isolated and persistent acquired edema localized exclusively to the genital area in recovering premature "Feeder and Grower" infants is however unusual and not systematically described in the medical literature.

Therefore, to our knowledge, this small case series of six neonates with late onset acquired isolated genital-area edema, is the first.

Patients and methods

We reviewed all infants with a diagnosis of edema in our 16-bed community level-3 NICU-database over a 10+-year period (January 2007–December 2017). We found a total of six patients having localized genital-area edema. All patients were ELBW, born between 2012 and 2017 and with birth weights ranging between 600 and 840 g and gestational ages ranging between 24 and 31 completed weeks. Five out of six infants were male. Potentially contributing factors were identified (Table 2).

Table 2: Pertinent characteristics of the six cases.

	Case 1	**Case 2**	**Case 3**	**Case 4**	**Case 5**	**Case 6**
GA (weeks)	31 + 5/7	25 + 2/7	25 + 5/7	24 + 3/7	30 + 1/7	24 + 2/7
BW (g)	783	600	840	760	740	790
Sex	Male	Female	Male	Male	Male	Male
SGA/IUGR	Yes	No	No	No	Yes	No
IH	No	No	Yes	No	Yes	Yes
DOL of IH diagnosis	N/A	N/A	69	N/A	45	63
DOL of IH repair	N/A	N/A	90	N/A	121	108
LE-PICC	Yes	No	No	No	Yes	Yes
DOL duration of LE-PICC	1–22	N/A	N/A	N/A	7–45	9–19
DOL at edema-diagnosis	67	>50	66	84	45	62
DOL at edema resolution	Beyond d/c	Beyond d/c	112	117	Beyond d/c	84
Extent of edema	– Pubic – Penile	– Pubic – Clitoral	– Pubic – Penile	– Penile	– Suprapubic – Pubic – Penile	– Penile
s-Na during hospitalization (meq/L)	132–139	125–143	127–146	129–151	124–146	125–155
s-Na at diagnosis (meq/L)	139 (DOL #71)		140 (DOL #65)	139 (DOL #54)	133 (DOL #44)	139 (DOL#48)
s-Na after diagnosis (meq/L)	138		136–138		131–137	138–141

s-Alb (g/dL)	2.9 (DOL #70)	2.0–2.2 (DOL #44–45)	3.0 (DOL#54)
s-TP (g/dL)		4.6 (DOL #45)	

Results

Patients

Case 1

The patient was a 31 + 5/7 weeks' gestational age small-for gestational age (SGA)/intra-uterine growth retarded (IUGR) male infant with birth weight of 783 g. Co-morbidities included trisomy 21, atrial septal defect (ASD), respiratory distress syndrome (RDS), mild right sided-hydronephrosis, glandular hypospadias and suspected sepsis treated with a 7-day course of antibiotics. A lower extremity percutaneous intravascular central catheter (LE-PICC) was placed on day of life (DOL) #1 and removed on DOL #22. Proper placement of the catheter tip at the level of the diaphragm was documented by radiograph at the time of insertion and again on DOL #7. Other imaging studies included an abdominal ultrasound that documented normal echo-texture of the liver and mild hydronephrosis. On DOL #67 the infant presented with penile and pubic edema that gradually resolved over the next 11 days. At discharge on DOL #78, only mild penile edema persisted. S-Albumin on DOL #70 was normal (2.9 g/dL) and s-Na was 139 meq/L.

Case 2

The patient was a 25 + 2/7 weeks' gestational age appropriate for gestational age (AGA) female infant with a birth weight of 600 g. Co-morbidities included RDS, stage 2 retinopathy (ROP) and a patent ductus arteriosus (PDA) that remained open but small at discharge. The infant had four suspected episodes of sepsis, each treated with empiric antibiotics for 7 days. Parenteral nutrition was provided for the first 30 days of life via an upper extremity PICC. Localized hard organized (brawny) pubic and clitoral edema developed during the second half of the 102-day long hospital stay and was still present at discharge.

Case 3 [Figure 1]

The patient was a 25 + 5/7 weeks' gestational age AGA male infant with a birth weight of 840 g. Co-morbidities included RDS, stage 2 ROP and a PDA that closed following early and prophylactic Ibuprofen treatment. The infant had umbilical catheters in place and reached full enteral feedings by DOL #10. The infant had two suspected episodes of sepsis, each treated with empiric antibiotics for 7 days. No PICC line was ever inserted.

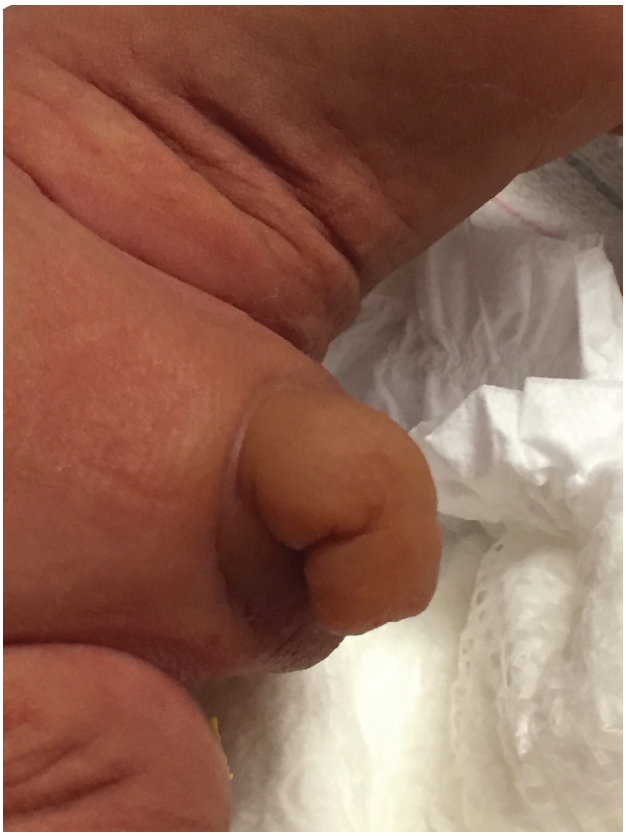

Figure 1: Case 3. Penile and pubic edema.

On DOL #66 the infant presented with penile and pubic edema and on DOL #69 a clinical diagnosis of bilateral inguinal hernias (IH) was made and confirmed by scrotal ultrasound. The IH were subsequently repaired on DOL #90 and the edema thereafter slowly subsided with the pubic swelling resolving first and the penile edema lasting until DOL #112. S-Na at diagnosis of edema and thereafter were normal.

Case 4 [Figure 2]

The patient was a 24 + 3/7 weeks' gestational age AGA male infant with a birth weight of 760 g. Co-morbidities included RDS, stage 2 ROP and a left tibial spiral fracture due to osteopenia. The infant had umbilical catheters in place and reached full enteral feedings by DOL #11. No PICC line was inserted.

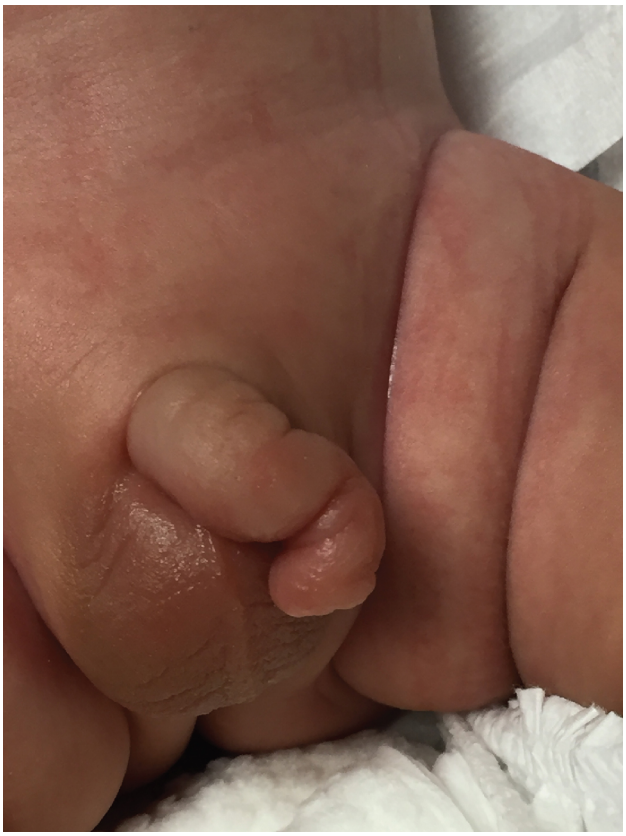

Figure 2: Case 4. Penile edema.

Isolated penile edema developed on DOL #84 and persisted until DOL #117. The infant had no clinical evidence of IH.

Case 5 [Figure 3]

The patient was a 30 + 1/7 weeks' gestational age SGA/IUGR male infant with a birth weight of 740 g. Comorbidities included RDS, methicillin-resistant *Staphylococcus aureus* (MRSA) – sepsis and pneumonia, cholestasis, thrombocytopenia and persistent polymicrobial Gram-negative bacteremia requiring lengthy treatment with antibiotics, severe chronic lung disease (CLD) and pulmonary hypertension. The infant also developed a left-sided humerus fracture due to osteopenia. A LE-PICC line was continuously in place first in the right and then in the left lower extremity between DOL #7–45. On DOL #45 the infant suddenly developed hard suprapubic, pubic and penile edema (Figure 3). The PICC was removed and ultrasound of the scrotum revealed large bilateral IH. The infant was extubated the next day (DOL #46) after a Dexamethasone course according to DART protocol but required re-intubation on DOL #91 due to severe hypercapnia. Repeat extubation attempts on DOL #97, 104 and 106 were unsuccessful for the same reason and a 2nd Dexamethasone course was initiated. The infant subsequently underwent IH-repair and gastrostomy-tube placement on DOL #121. The edema remained relatively unchanged at the time of transfer to another hospital on DOL#135 for pulmonary consultation regarding the need for tracheostomy, following a 5th unsuccessful extubation attempt. S-albumin ranged between 2.0 and 2.2 g/dL, s-total protein was 4.6 g/dL and s-Na 133 meq/L at the time of diagnosis. S-Na subsequently ranged between 131 and 137 meq/L.

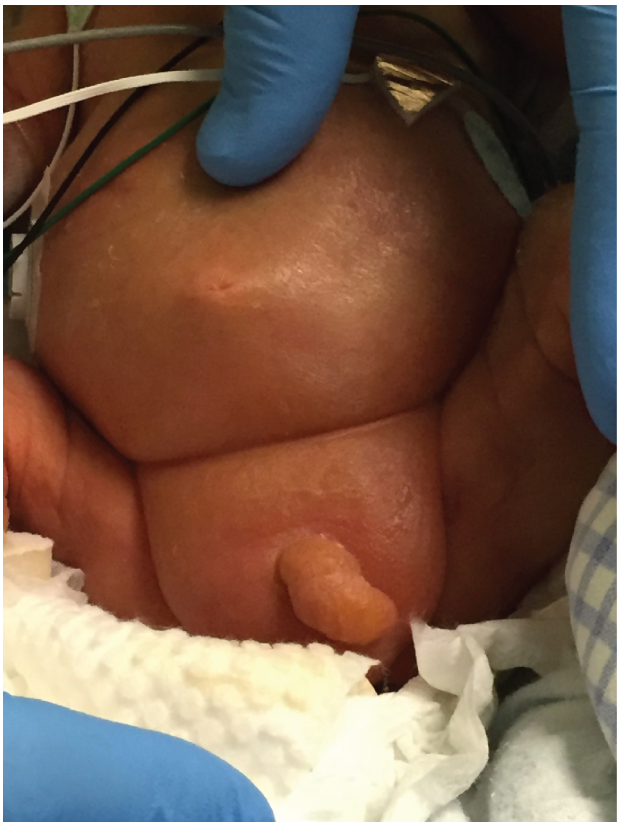

Figure 3: Case 5. Penile, pubic and suprapubic edema.

Case 6

The patient was a 24 + 2/7 weeks' gestational age large for gestational age (LGA) male infant with a birth weight of 790 g.

Co-morbidities included RDS, stage 2 ROP and coagulase-negative staphylococcal (CONS) sepsis for which the infant received a 19-day course of vancomycin. The infant had a PICC in place in the right lower extremity for 11 days that was removed on DOL #19. Isolated penile edema developed on DOL #62 and resolved by DOL #84.

A right IH was clinically diagnosed on DOL #63, confirmed by ultrasound on DOL #86 and repaired on DOL #108.

S-Na was normal prior to and after the diagnosis of edema. S-albumin prior to diagnosis of edema was normal.

Discussion

Congenital lymphedema of the external genitalia is rare, presents at birth and rarely regresses [3].

Primary lymphedema of the genitalia is also rare. The extremity is the most common site of involvement (82%), especially the lower extremity (92%). In a series of 138 pediatric patients with primary lymphedema, only 4.3% (six cases and all male) involved exclusively the external genitalia [4]. Among 23 boys with primary genital (i.e. peno-scrotal) lymphedema, 14 presented in infancy, but more than three-quarters also had lower extremity involvement. Only four had isolated genital involvement [5].

However, as mentioned all edema is not necessarily lymphedema. We do not actually know whether our six cases represent primary lymph edema, edema from increased hydrostatic pressure or capillary leak.

Our six infants had normal external genitalia at birth, no involvement of the lower extremities, no other signs of congenital lymphatic conditions such as cystic hygroma or chylothorax and they subsequently and rather suddenly developed organized or "brawny edema" due to accumulation of fluid within the pubic-phallic interstitial spaces. This brawny edema should not be confused with *sclerema neonatorum*, a rare condition seen in critically ill infants and which is characterized by hardening of the skin which gets fixed to the underlying

tissues and leads to death in the majority of cases. Palms, soles and genitalia are characteristically spared in this condition. In contrast, *scleredema*, which is a self-limiting condition occurring within the first week of life in premature infants, is characterized by generalized pitting edema and is associated with infection [6].

Our six cases of pubic-phallic edema occurred at much later post-natal ages and in recovering "Feeder-Growers."

Genital edema has been described in a 24-weeks' gestational age infant as a complication of a femoral venous catheter but resolved within hours of removing the catheter [7]. Likewise, a case of peno-scrotal edema in a 32-weeks' premature infant as a complication of a LE-PICC line inadvertently inserted into a spermatic vessel resolved within hours of removing the catheter [8].

These mechanisms do not explain our three cases with LE-PICC, which presented either after a relatively long period of time following LE-PICC line removal (Cases 1 and 6), or persisted long after its removal (Case 5). Second, all of our LE-PICC lines are inserted at or below the knee and we do not use direct femoral access. Third, the position is always documented with a two-view chest-abdominal radiograph, fourth, LE-PICC lines have a lot of leeway with their position within the inferior vena cava and are unlikely to migrate into genital area vessels following initial correct placement and fifth, three cases (#2, 3 and 4) had no history of ever having had a LE-PICC-line placed.

We can perhaps speculate that cases 3, 5 and 6 could have been at least in part caused by mechanical obstruction of local venous drainage and/or lymphatic flow from a mass effect exercised by the IH (especially the large bilateral IH of case 5), which are often associated with hydroceles. However, scrotal edema in addition would be expected. A 32-weeks' gestational age 1700 g birth weight premature infant developed isolated peno-scrotal edema at 1 month of age and the edema remained unchanged until 4 months of age when gradual resolution began. The infant had a small congenital hydrocele, which remained after the edema resolved [9].

Large abdomino-scrotal hydroceles causing lower extremity edema (but not isolated genital edema) through mechanical compression of the femoral triangle or ileac vessels have been described [10], [11], [12].

Our six cases all occurred in stable recovering premature infants on full enteral feedings whose clinical status allowed for different sleeping positions and upright holding. Therefore, positioning alone could not reasonably explain the edema. None of the male subjects had undergone a circumcision. We only have information about serum albumin levels in three patients (2/3 were within normal limits) as we do not routinely check those. However, none of the patients had evidence of cardiac, renal or liver failure. The sodium concentrations were within expected ranges for this patient population and no patient at the time of edema presentation had evidence of infection. Thus, a systemic inflammatory or third-spacing process seems non-plausible.

No patient had any history or clinical signs of venous thrombosis or venous stasis and one would especially expect to see lower extremity swelling in addition to the genital-area edema, in the cases were a LE-PICC line was present and if it was the culprit. Only one patient was dysmorphic (Case 1: trisomy 21). Although lymphatic malformations are known to accompany this condition, no clinical evidence of such was present at birth. The sudden onset and the rapid development of hard edema rather than long-standing pitting edema gradually evolving into brawny edema, would perhaps suggest a more rapid leak of plasma proteins and thus most consistent with a local inflammatory process. However, no concomitant dermatitis was present and a reaction to diaper material or topical skin barrier agents would be expected to involve perianal and gluteal areas as well.

Conclusions

This is a small retrospective study of six infants with unexplained isolated genital area edema. We cannot conclude whether these cases represent a symptom stemming from different etiologies, a previously not described distinct clinical entity, or simply very unusual manifestations of primary lymphedema. The sudden occurrence and prolonged duration of edema in stable recovering premature infants on full enteral feedings and with s-Na within expected range makes a systemic inflammatory or third spacing process unlikely.

Previous case series have focused on either primary lymphedema or male genital lymphedema in a wide pediatric population (<21 years of age) but the number of infants is small [4], [5]. Our small series is the first analyzing potentially contributing factors of isolated genital-area edema as a symptom in an exclusively neonatal population. We do not have any information of the post-discharge course of these infants but we do have a very close working relationship with our local community primary care physicians and we have seen no re-admissions to our pediatric service and received no phone calls about concerns regarding complications of genital area edema.

Given the rarity of this manifestation (six cases among 54 ELBW-infants out of a total of 1306 NICU admissions over a 5-year period) and the limited techniques available to actually image the lymphatic system and establish a definite diagnosis of lymphedema, we feel that cautious expectant management and reassurance

are warranted (once scrotal ultrasound has ruled out sub-clinical IHs and abdominal radiographs have ruled out mal-position of a vascular catheter) as no detrimental effects of the edema (such as urinary retention or skin break down) were seen during these infants' prolonged stay in the NCIU.

Author's Statement

Conflict of interest: The authors state no conflict of interest.

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