CASE REPORT

Acute lymphoblastic leukaemia presenting with galactorrhoea

Wing Shan Queenie See, Daniel Ka Leung Cheuk, Kong Lam Marcus Fung, Godfrey Chi Fung Chan

Department of Paediatrics & Adolescent Medicine, The University of Hong Kong, Hong Kong, Hong Kong

Correspondence to
Professor Godfrey Chi Fung Chan, gcfchan@hku.hk

SUMMARY

A teenage girl presented with galactorrhoea and moderate hyperprolactinaemia. She was subsequently diagnosed to have acute lymphoblastic leukaemia. Further investigations supported the presence of ectopic prolactin production as suggested by the presence of prolactin mRNA in the patient's marrow at diagnosis. Both the ectopic prolactin mRNA and galactorrhoea eventually resolved upon disease remission after treatment.

BACKGROUND

Galactorrhoea is a rare initial presentation feature of acute leukaemia. There were a few case reports suggesting that this might be caused by ectopic prolactin production by leukaemic blasts in patients with acute myeloid leukaemia but no conclusive evidence can be drawn. This is the first report of galactorrhea as presenting symptom in patients with acute lymphoblastic leukaemia (ALL) and we found that ectopic prolactin was mainly derived from marrow, possibly leukaemic blasts. Aware of this association can help to avoid delay in diagnosis and unnecessary investigations.

CASE PRESENTATION

A 13-year-old girl presented with 1-week history of symptomatic anaemia, galactorrhoea, tarsometatarsal joint pain and swelling. On physical examination, she had pallor, right postauricular lymphadenopathy, swollen and tender left tarsometatarsal joint and bilateral galactorrhoea. There was neither hepatosplenomegaly nor neurological deficit. She also did not have any sign of meningeal irritation suggestive of central nervous system (CNS) involvement.

INVESTIGATIONS

Peripheral blood revealed anaemia with haemoglobin 7.2 g/dl, thrombocytopenia with platelet 36×10^9/l and peripheral blasts of 1.2×10^9/l (21% of total white blood cells). High cell turnover was evident by hyperphosphataemia, elevated lactate dehydrogenase (>6450 U/l) and hyperuricaemia (460 umol/). Bone marrow aspiration and trephine biopsy showed markedly hypercellular marrow packed with blasts with significantly reduced normal haematopoietic precursors. Many of the blasts showed varying degree of terminal deoxynucleotidyl transferase positivity consistent with ALL. Immunophenotyping confirmed CD10 positive B-lineage ALL and cytogenetics showed t(11;19). Prolactin level was 2239 mIU/l (reference: <500 mIU/l) and the assay was negative for macroprolactin. Oestradiol, luteinising hormone, follicular-stimulating hormone, thyroxin and thyroid stimulating hormone were all normal. Lumbar puncture and MRI brain were performed and there was neither any evidence of leukaemic infiltration of the pituitary nor the presence of concomitant pituitary tumour.

DIFFERENTIAL DIAGNOSIS

While the diagnosis of ALL was unequivocal, the cause of her galactorrhoea remained uncertain. The differential diagnoses of her galactorrhoea included CNS infiltration of the pituitary gland causing aberrant prolactin secretion; concomitant CNS prolactin secreting pituitary tumour; ectopic prolactin produced by bone marrow microenvironment either from the blasts or marrow stromal cells.

TREATMENT

Induction chemotherapy according to ALL Children's Cancer and Leukaemia Group 2008 protocol (modified from BFM-ALL 2002 protocol) was started, which consists of prednisolone, vincristine, daunorubicin and L-asparaginase. Galactorrhoea gradually subsided in the second week of treatment, and prolactin level on day 13 showed a significant reduction to 110 mIU/l, which is within normal limits. Repeated bone marrow examination on day 33 documented disease remission. Immunohistochemical staining failed to show the presence of prolactin in the blasts from the diagnostic bone marrow aspirate but reverse transcriptase PCR (RT-PCR) of the same specimen using a prolactin cDNA specific primer[1] confirmed that there was active ectopic prolactin transcription occurring in the bone marrow at diagnosis. Repeated RT-PCR showed disappearance of the prolactin mRNA in bone marrow aspirate on day 33 (figure 1). This implied such process gradually resolved when the disease went into remission.

OUTCOME AND FOLLOW-UP

After induction chemotherapy, the patient went on to receive intensification, consolidation and maintenance chemotherapy. She was in continuous complete remission with no evidence of minimal residual disease by both flow cytometry and immunoglobulin gene rearrangement detection. RT-PCR also showed disappearance of her aberrant chimeric transcript. There was no recurrence of galactorrhoea at 11th-month follow-up from initial diagnosis.

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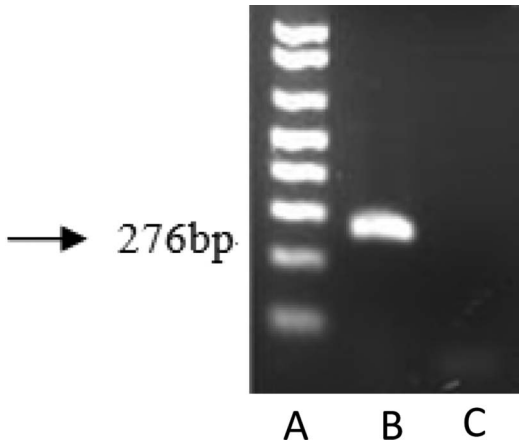

Figure 1 Gel electrophoresis analysis of amplified cDNA for prolactin gene expression of bone marrow cells before and after chemotherapy. Primer used in PCR would amplify a 276 bp segment in prolactin cDNA. Lanes (A)–(C) were DNA 100 bp ladder, (B) patient's bone marrow sample at diagnosis, (C) patient's bone marrow sample after acute lymphoblastic leukaemia D33 protocol, respectively.

DISCUSSION

Galactorrhoea refers to the secretion of milky discharge from the breast. It can be physiological or pathological. Sakiyama and Quan[2] described 0.1–32% prevalence of galactorrhoea in women with 49–77% of these attributed to non-puerperal hyperprolactinaemia. Pituitary tumours account for 20% of all cases of galactorrhoea and 34% of cases of amenorrhoea galactorrhoea.[2]

The normal prolactin level for non-pregnant and non-lactating women is less than 1180 mIU/l. During pregnancy at term, the prolactin level rises to around 9000 mIU/l and for postpartum lactation, the level of prolactin is around 2400–4800 mIU/l.[3 4]

Our teenage patient with ALL presented with galactorrhoea and a relatively low prolactin level of 2239 mIU/l. Normal MRI of the pituitary and cerebrospinal fluid ruled out the possibility of pituitary tumours or pituitary infiltration of the leukaemic blasts. In addition, galactorrhoea caused by pituitary overproduction is usually associated with a much higher level of prolactin associated with increase in macroprolactin level. We detected active ectopic prolactin mRNA transcription from the diagnostic bone marrow samples, suggesting the ectopic prolactin is derived either from the leukaemic blasts or from the marrow stromal cells.

There have been three previous reports of haemic malignancies presented with galactorrhoea. They were all adult female patients: one had T-cell leukaemia[5] and two had acute myeloid leukaemia.[6 7] All three case reports described an association of galactorrhoea with leukaemia in the absence of pituitary tumour or leukaemic infiltrates of the pituitary. Their clinical information is summarised in table 1. All of them had galactorrhoea and hyperprolactinaemia but there was no evidence of pituitary abnormality. They were not able to demonstrate the origin of the ectopic prolactin but based on our observation, it is likely derived from the marrow microenvironment in particularly the leukaemic blasts.

The galactorrhoea as well as the hyperprolactionaemia resolved after treatment of the leukaemia in two of the three reported cases. This supports the hypothesis of leukaemia associated ectopic hyperprolactinaemia which in turn results in galactorrhoea. In the absence of hypophyseal and hypothalamic lesion, ectopic prolactin secretion is most likely.

A series of 28 patients with acute myeloid leukaemia (M1–M6) were screened for pituitary hormonal levels.[8] Sixteen of 28 had significantly elevated prolactin level while other hormones were normal. The elevated prolactin may be due to stress but one patient with subtype M4 and hyperprolactinaemia demonstrated ectopic synthesis of prolactin in the blast cells (as a growth stimulant of the leukemic myeloblast) by immunoblotting.[8] This supports extrapituitary prolactin production in leukaemic blasts.

However, immunohistochemistry failed to detect prolactin in the blast cells in case 3 reported by Muslahi. According to Bellone *et al*[9] bone marrow stromal cells can synthesise prolactin. Hence Muslahi suggested that prolactin production can be upregulated by release of cytokines due to the interaction of blasts cells and other cells in the marrow.

On the other hand, Reem *et al*[10] revealed that the upstream promoter of prolactin gene in human is regulated in lymphoid cells by activators of T cells and cAMP. Gerlo *et al*[11] then demonstrated that the promoter activates prolactin expression in the myeloid leukaemic cells by tumour necrosis factor-α. In our case of ALL, we tried to detect the presence of prolactin in the leukaemic blasts as previously demonstrated.[8 12] However, we were unable to demonstrate the presence of prolactin in blasts by immunohistochemical method. Whether this method has adequate sensitivity to detect the low level of intracellular secretion of prolactin remains to be verified. We also used the bone marrow aspirate at diagnosis and on remission (day 33) for the detection of the extrapituitary prolactin gene expression. The result was appealing as it was positive at diagnosis and negative on remission. This signifies a clinical correlation to support the hypothesis of extrapituitary prolactin production by the leukemic blasts. However, the possibility that prolactin is also expressed from marrow stromal cells cannot be excluded at this moment.

Of note is that in the case reported by Matsumura (case 1), hyperprolactinaemia and galactorrhoea persisted despite the initial remission of leukaemia. This may suggest persistent minimal residual disease with continuous ectopic production of prolactin. This is supported by the fact that the disease relapsed 4 months later in that case.

Table 1 Clinical information of previous reported cases of leukaemia with galactorrhoea

Case (ref)	Patients (years)	Dx	Presenting features	Hyperprolactinaemia	Hypophysis and hypothalamic lesion	Regress with Rx	Level of prolactin (mIU/l)
1 (v)	F/48	T-ALL	Lumbago and galactorrhoea	Yes	Neg (CT & MRI)	No	NA
2 (vi)	F/21	AML	Galactorrhoea	Yes	Neg (CT)	Yes	7887
3 (vii)	F/40	AML	Galactorrhoea	Yes	Neg (CT & LP)	Yes	4158

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; Dx, diagnosis; F, female; NA, not available; neg, negative; ref, references.

In summary, we reported the first adolescent ALL patient with galactorrhoea due to ectopic production of prolactin in bone marrow, likely from the leukaemic blasts, which resolved upon remission of leukaemia. Though uncommon in ALL, we should be aware of such presenting feature so delay in diagnosis and unnecessary investigations can be avoided. Whether ectopic hyperprolactinaemia is associated with a rare subgroup of ALL and the detailed molecular mechanisms of induction of ectopic prolactin gene expression remain to be elucidated in the future.

Learning points

- Galactorrhoea is a rare initial presentation of acute leukaemia due to ectopic hyperprolactinaemia.
- Absence of hypophyseal and hypothalamic lesion supports ectopic production of prolactin.
- Gel electrophoresis analysis of amplified cDNA for prolactin gene expression of bone marrow cells in our case supports the activation of prolactin expression by the prolactin gene promoter in marrow microenvironment possibly lymphoid leukaemic cells.
- Further study of increased prolactin gene expression aids in-depth understanding of the properties of the leukaemic cells.
- Normalisation of prolactin level and resolution of ectopic prolactin gene expression may be an indicator of treatment success.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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