Obstetrics Gynaecology 2020: Cerebrocostomandibular Syndrome - A case report- Dr Anupriya Gupta- North Middlesex University Hospital, London, U K

Abstract

We report a postnatal diagnosis of cerebrocostomandibular Syndrome (CCMS) in a new born after a low risk pregnancy. The dating scan, combined test and anomaly scans were normal. Polyhydramnios was noted at 28 weeks (amniotic fluid index: 28.2mm). The mother delivered by an emergency Caesarean for failure to progress.

The female baby was born through thick meconium and required 3-4 mins of resuscitation. She was noted to have dysmorphic features (micrognathia, submucosal cleft palate, bilateral sacral dimples, left ear pit, anteriorly positioned anus). Further evaluation made a diagnosis of CCMS secondary to a de novo mutation. We discuss this rare syndrome and undertake a literature search for isolated micrognathia. The anomaly check in the UK follows the National screening committee and Fetal anomaly screening programme (FASP) guidelines. FASP recommends a mid-pregnancy scan which is undertaken between 18+0 to 20+6weeks to screen for major fetal anomalies. The main structures to be assessed between these weeks are defined. Abnormalities of these structures can indicate a number of specific conditions. Coronal view of lips with nasal tip are viewed but not the sagittal view of the face. If micrognathia is the only sonographic finding identified, physicians

and families should be prepared for possible respiratory difficulty at delivery, the presence of a cleft palate, and/or developmental delay.

Introduction

The increasing number of genetic alterations discovered in acute myeloid leukemia (AML) has not only increased our understanding of this heterogeneous disease but also provided prognostic information through which individualized treatment for the best interests of patients may become possible. These impacts of genetic mutations have been underscored by the inclusion of NPM1 and CEBPA mutations in the 2008 World Health Organization classification of AML.

Among these genetic alterations, mutations of Isocitrate dehydrogenase 1 (IDH1) and IDH2, which encode two isoforms of isocitrate dehydrogenase, are special in that these genes are involved in metabolism, 1, 2 rather than signaling pathways or transcription factors, which are commonly deranged in AML. The clinical and biological characterization of IDH mutations in myeloid malignancies have been reported in several studies. IDH mutations occur at low frequencies (3.6-5%) in myelodysplastic syndrome, 3, 4 and chronic-phase myeloproliferative in

neoplasm (about 1.8%),5, 6 but obviously increased as these diseases progress to AML (7.5–21%),3, 4, 5, 6 indicating a role of IDH mutations in leukemogenesis. In IDH2 mutations occur more AML, frequently than IDH1 mutations, with frequencies of 11 vs 6% in patients younger than 60 years,7 15.4 vs 7.7% in total patients,8 and 19 vs 14% in adults with normal karyotype.9 Although IDH1 and IDH2 proteins locate differently, in cytosol and mitochondria, respectively, they both function to generate α ketoglutarate and are supposed to control redox status in cells.10, 11 The IDH mutants gain the neomorphic enzyme activity and lead to the production of an onco-metabolite, 2-hydroxyglutarate (2-HG), which was speculated to upregulate hypoxia-inducing factor 1α by inhibition of prolyl hydroxylase.1, 2, 10, 12

On the basis of the in vivo functions of IDH1 and IDH2, it is intuitive to expect similar clinical and biological characteristics between AML bearing mutations of these two genes. Indeed, mutations of both genes are more commonly present in patients with normal cytogenetics.7, 13, 14, 15. 16. 17 However. different features between IDH1-mutated and IDH2-mutated AML were shown in several reports, and even there existed differences between IDH2 R140 and R172 mutations.9, 17, 18 In addition, the prognostic implications of these mutations also varied widely among different institutions.7, 15, 17 More perplexingly, IDH2 R172 mutation alone was found to have distinct gene- and microRNA-expression profiles,9 and appeared to be an independent poor prognostic factor.18 In contrary, results from two studies suggested a possible favorable impact of IDH2 mutation in subgroups of AML patients.7, 8 Overall, the prognostic implication of IDH2 mutation is still controversial. Moreover, the side-by-side comparison is needed to

delineate the similarities and distinctions among mutations at IDH1 R132, IDH2 R140 and IDH2 R172. Finally, the stability of IDH2 mutation remains uninvestigated.

We have previously reported the clinical and biological characteristics of AML patients with IDH1 mutation at R132.14 To further clarify the above issues of IDH1 and IDH2 mutations in AML, we then analyzed 446 adults with non-M3 AML in our institute. We found that IDH2 mutations were associated with some distinct biological features and implicated a longer overall survival (OS) in all non-M3 patients and in those with a normal karyotype. Moreover, IDH2 mutation was an independent favorable prognostic factor in multivariate analysis. Finally, by a comprehensive sequential study, we confirmed that IDH2 mutation, like IDH1 mutation we previously described, 14, 19 was a stable mutation during disease evolution.

Materials and methods

Patients

From 1995 to 2007, a total of 674 adult patients with de novo AML were diagnosed the National at Taiwan University Hospital according to the French-American-British Cooperative Group Criteria. There were 497 patients with cryopreserved bone marrow cells and complete clinical and laboratory data for These patients analysis. 497 were representative of the whole cohort because the clinical data and treatment outcome were not different from the whole population (data not shown). Patients with AML M3 subtype were not included in the study because of their distinct treatment and prognosis. Therefore, a total of 446 adult patients (≥ 18 years) were included in this study. Written informed consent in accordance with the Declaration of Helsinki was obtained from all participants and the study was approved by the Institutional Review Board of the National Taiwan University Hospital. The bone marrow cells were collected serially at the time of diagnosis, after chemotherapy and at relapse. Among these 446 patients, 309 patients (69.3%) received conventional chemotherapy induction (idarubicin 12 mg/m2 per day on days 1-3 and cytarabine 100 mg/m2 per day on days 1followed consolidation 7), by chemotherapy with 2-4 cycles of highdose cytarabine (2000 mg/m2 every 12 h on days 1-4, total eight doses) with or without an anthracycline (idarubicin or mitoxantrone) after achieving complete remission (CR). The remaining 137 patients received palliative therapy or lowdose chemotherapy because of poor performance status or per patients' wish.

Mutation analysis

Mutation analyses were performed on CEBPA in the only exon, 20 WT1 in exons 7, 8 and 9,21 MLL-PTD that spanned exons 2-8,22JAK2 on V617F hot spot,23 PTPN11 in exons 3 and 13,24 RUNX1 in exons 3-8,25 c-KIT in exons 8, 10, 11, 12 and 17,26 RAS on codons 12 and 13, and 61 in exons 1 and 2,27 FLT3-TKD on codon D835,28 IDH1 on R132 hotspot,14 ASXL1 in exon 12,29 NPM1 on hotspot involving the C terminal portion of the transcript with a four nucleotides insertion between positions 960 and 961,30 and FLT3-ITD in exon 1431 as described previously. Mutations were detected by direct sequencing on the PCR products, and the sensitivity of each assay was about 15%.

Gene cloning

When IDH2 mutations detected at diagnosis were absent in relapsed bone marrow samples by direct sequencing, we

performed TA cloning (Yeastern Biotech, Taipei, Taiwan) of the PCR products spanning the mutation hotspots, followed by sequencing of individual clones to search for any mutation.

Cytogenetic analysis

Bone marrow cells were harvested directly or after 1–3 days of unstimulated culture. Metaphase chromosomes were banded by the G-banding method as described previously.32

Immunophenotyping

A panel of monoclonal antibodies, including myeloid-associated antigens (CD13, CD33, CD11b, CD14, CD15 and CD41a), as well as lymphoid-associated antigens (CD2, CD5, CD7, CD19, CD10 and CD20), and lineage-nonspecific antigens (HLA-DR, CD34 and CD56), was used to determine the immunophenotypes leukemia previously of cells as described.33

Statistics

The χ^2 test was used to compare discrete variables of patients with and without gene mutation. Fisher exact test was used for comparing the incidence of IDH2 mutation between different cohorts. Mann-Whitney test method was used to compare continuous variables and medians of distributions. Only 309 patients who received conventional induction chemotherapy subsequent and consolidation chemotherapy after achieving CR were included in the survival analysis. OS was measured from the date of first diagnosis to the date of last follow-up or death from any cause. Kaplan-Meier estimation was used to plot survival curves, and log-rank tests were used to calculate the difference among groups. Patients receiving hematopoietic transplantation were censored on the day transplantation. Multivariate of Cox proportional hazard regression analysis

was used to investigate independent prognostic factors for OS. A P-value <0.05 was considered statistically significant. All statistical analyses were performed using the SPSS 17 software (SPSS Inc., Chicago, IL, USA).

Results

IDH2 R140 and R172 mutations

These 446 non-APL patients consisted of 251 males and 195 females, with a median age of 53 years (range, 18–90 years). The IDH2 mutation was detected in 54 patients (12.1%), including 13 (2.9%) with R172 mutation and 41 (9.2%) with R140 mutation, whereas the IDH1 mutation was found in 27 patients (6.1%).

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