Atypical Ph negative chronic myeloid leukaemia presenting as sudden profound deafness

N Smith, B Bain, L Michaels, E Craven

Abstract
A patient with atypical Ph negative chronic myeloid leukaemia presented with the sudden onset of profound deafness. He survived only eight months. Detailed histological investigation performed at necropsy showed loss of ganglion cells and afferent nerve fibres in the cochlea and vestibule associated with extensive fibrosis and new bone formation in the labyrinthine spaces. Both leukophoresis and high dose chemotherapy capable of rapid cyto reduction are recommended in patients with chronic myeloid leukaemia with profound hearing loss, as conventional chemotherapy is rarely followed by recovery.

Deafness can occur in patients with acute myeloid leukaemia or the blastic phase of chronic myeloid leukaemia (CML) and is usually due to leukaemic infiltration, though sometimes to infection or haemorrhage. It is very rare in the chronic phase of either Philadelphia chromosome (Ph) positive or negative CML, and in this situation is usually attributed to hyperviscosity leading to vascular occlusion. Patients with Ph negative CML who lack the Ph chromosome, who may or may not have a rearrangement of the break-point cluster region of chromosome 22, may show features similar to classic Ph positive chronic granulocytic leukaemia (CGL) or have recognisably different features such as refractoriness to chemotherapy and a short survival.

Case report
A 62 year old man developed mild deafness and tinnitus in his left ear over two months with associated malaise and weight loss. His deafness increased over three days becoming almost complete at presentation. He had a low grade fever and hepatosplenomegaly but no lymphadenopathy. He had almost complete bilateral hearing loss, bilateral primary horizontal and vertical nystagmus, decreased left facial movement, and absent jaw jerk and gag reflex. He had bilateral fundal soft exudates but no haemorrhages or hyperviscosity changes. His haemoglobin concentration was 11.5 g/l, white cell count 156 x 10^9/l with 51% neutrophils, 3% lymphocytes, 12% monocytes, 2% metamyelocytes, 30% myelocytes and occasional promyelocytes. The platelet count was 603 x 10^9/l and neutrophil alkaline phosphatase score was 140 (normal range 35-100). A marrow aspirate was hypercellular with increased granulopoiesis. Bone marrow cytogenetics showed a normal 46 XY karyotype and DNA analysis showed no BCR rearrangement. Analysis of cerebrospinal fluid yielded normal results. Audiometry confirmed severe bilateral sensorineural deafness with minimal residual hearing at low frequency in the right ear.

He was treated with cytosine arabinoside, hydroxyurea and busulphan but responded poorly. He had minimal recovery of hearing in his right ear. He died suddenly eight months after diagnosis.

Histological findings
Post mortem examination showed hepatosplenomegaly with severe pulmonary oedema. The auditory nerves were grossly normal. Temporal bone histology showed that two thirds of the right scala tympani of the cochlear basal coil had been obliterated by myxoid fibrous tissue which also partly replaced the modiolus and vestibule (Figure). Spiral ganglion cells were absent in the apical and middle coil regions of the modiolus and reduced in the basal coil region. Basilar membrane nerve fibres were greatly reduced. The organ of Corti was atrophic with hydrops in the cochlear duct of each coil. The vestibule had also been replaced by myxoid fibrous tissue with some new bone formation around its periphery. The wall of the lateral semicircular canal was thickened by bone and its lumen occluded by fibrous material. The maculae of the saccule and utricle were absent. The vestibular nerves were atrophic with a loss of vestibular ganglion cells in the internal auditory meatus. The superior and posterior semicircular canals were fibroser. The left temporal bone showed similar though less extensive changes with myxoid fibrous tissue in the scala tympani and semicircular canal fibrosis. Brain histology was normal.

Discussion
Our patient with Ph negative CML followed the usual clinical course with refractoriness to chemotherapy and a short survival. His deafness seems related to the leukaemia with a close temporal relationship to the onset of disease and some recovery of hearing on lowering the white cell count. Deafness is rare in chronic phase CML, usually being attributed to hyperviscosity; the presenting white count in our patient was uncharacteristically low, counts in previous reported cases ranging from 210 to 1288 x 10^9/l.

The mechanism of the deafness in our patient is uncertain. The sensory end organs of...
of infection in this patient. Hyperviscosity is unlikely to lead to such profound permanent changes affecting sensory and ganglion cells or labyrinthine structures. Haemorrhage could cause widespread labyrinthine changes but these are usually irregular. There was no evidence of haemosiderin or cholesterol granuloma at post mortem to suggest this as a cause. The most likely cause seems to be leukaemic infiltration of the labyrinthine spaces involving the perilymphatic space and basilar membrane; disappearance of leukaemic cells with treatment could be followed by extensive fibrosis and bony reaction with loss of sensory cells and their nerve supply. The cranial nerve palsies remain unexplained.

It is difficult to distinguish between deafness due to hyperviscosity or leukaemic infiltration in patients with AML. We advocate both leucopheresis and high dose chemotherapy capable of rapid cytoreduction, as conventional chemotherapy is rarely followed by recovery.


Pulmonary infarction, myocardial infarction, and acute disseminated intravascular coagulation

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Abstract

Pulmonary and myocardial damage are frequently cited as manifestations of disseminated intravascular coagulation (DIC), but rarely as causes. Three elderly cases of severe DIC due to pulmonary and myocardial infarction are reported. All three patients died. Necropsy showed extensive pulmonary emboli in each case with large pulmonary infarcts in cases 1 and 2 and a ventricular aneurysm containing thrombus in cases 2 and 3. Early diagnosis and treatment of pulmonary embolism requires a high degree of clinical suspicion but may prevent progression to the irreversible stage of severe DIC.

Disseminated intravascular coagulation (DIC) is characterised by inappropriate activation of the coagulation system, with consumption of coagulation factors and secondary fibrinolysis. It is not a single disease process, but a common pathway in a large number of primary disorders. Pulmonary and myocardial damage are frequently cited as manifestations of DIC, which we believe obscures the fact they also number among its causes.
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