Piebaldism

(Piebaldism)

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ABSTRACT
Background: Piebaldism is a rare autosomal dominant genetic disorder characterized by congenital life-long patches areas of depigmentation. This condition is due to an absence of melanocytes in affected skin and hair follicles as a result of mutations in the KIT gene on chromosome at 4q12. This mutation results in abnormal tyrosine kinase transmembrane receptors, decreases signal transduction, and causes abnormal melanocyte embryogenesis with defective melanoblast proliferation, migration and distribution. **Purpose:** To know the pathomechanism, characteristic sign feature (established diagnosis), differential diagnosis, and examination must be perform for this disease. **Case:** A 5-year-old javanese boy came to our department with depigmented patches. There were white patch on the central portion of forehead (white forelock), depigmented patches with islands of normally pigmented patches on the abdomen, hypopigmented patches with hyperpigmented borders on his both legs. The size and appearance of patches had remained unchanged since birth. No family history was noted. The result of laboratory tests, consultation to ENT department and Opthalmologic department were normal. Histopathology examination from depigmented area revealed the decreased number or absent melanocytes and melanosome granules. **Case management:** The management was the usage of sunscreen, camouflage and sun avoidance during peak hours of ultraviolet exposure during a day. **Conclusion:** Piebaldism is a benign disorder. Pigmentary alteration usually stable and permanent and patient can have normal life span. However, giving information about genetic inheritance and education of this disorder to the patients and family member must be done clearly.

Key words: piebaldism, white forelock, the c-kit gene

ABSTRAK
Latar belakang: Piebaldism adalah penyakit genetik *autosomal dominant* yang jarang dengan tanda khas bercak hipopigmentasi kongenital. Hal ini berkaitan dengan tidak adanya melanosit pada kulit dan rambut oleh karena mutasi gen KIT pada kromosom 4q12. Mutasi ini menyebabkan abnormal reseptor transmembran *tyrosine kinase*, penurunan sinyal transduksi dan abnormalitas embriogenesis melanosit dengan defek proliferasi melanoblast, migrasi dan distribusi. **Tujuan**: Mengetahui patomekanisme, tanda khas dan cara menegakkan diagnosis, diagnosis banding dan pemeriksaan yang harus di lakukan untuk penyakit ini. **Kasus**: Seorang anak laki-laki usia 5 tahun suku jawa datang dengan bercak depigmentasi. Bercak putih terdapat pada bagian sentral dari kulit dan rambut kepala (jambul), bercak depigmentasi dengan pulau-pulau dengan pigmentasi normal pada area abdomen, bercak hipopigmentasi dengan batas hiperpigmentasi pada kedua betis. Ukuran dan gambaran bercak tidak pernah berubah sejak lahir. Tidak ada riwayat keluarga dengan penyakit ini. Hasil uji laboratorium, konsultasi ke bagian THT dan Opthalmologi dalam batas normal. Pemeriksaan histopatologi dari area kulit leukoderma menunjukkan penurunan melanosit dan melanosome granul. **Penatalaksanaan:** Penatalaksanaannya adalah menggunakan tabir surya, kamuflase dan menghindari sinar matahari pada waktu puncak paparan sinar ultraviolet. **Kesimpulan:** Piebaldism adalah penyakit jinak. Perubahan pigmentasi biasanya bersifat stabil dan menetap dan pasien dapat hidup normal. Harus diberikan informasi dan edukasi yang jelas tentang penyakit ini pada pasient dan keluarganya.

Kata kunci: *piebaldism*, *white forelock*, *gen* KIT

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BACKGROUND

Piebaldism is a rare autosomal dominant disorder of melanocyte development characterized by a congenital white forelock and multiple symmetrical hypopigmented or depigmented macules. This striking phenotype of depigmented patches of skin and hair has been observed throughout history, with the first descriptions dating to early Egyptian, Greek, and Roman writings. The word piebald itself has been attributed to a combination of the "pie" in the magpie

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(a bird of black and white plumage) and the "bald" of the bald eagle (the United States' national bird, which has a white feathered head).[1]

Piebaldism is due to an absence of melanocytes in affected skin and hair follicles as a result of mutations of the kit proto-oncogene.[1,2,3,4] Both hair and skin are permanently white from birth or when hair color first becomes apparent.[1,5,6] The severity of phenotypic expression in piebaldism correlates with the site of the mutation within the KIT gene.[1,5,6]

Depigmented area on the forehead often include the whole or inner potions of the eyebrows and eyelashes and extend to the root of the nose. Hypopigmented or depigmented areas have also been noted commonly on the chin, anterior neck, anterior portion of the trunk and abdomen, and on the anterior and posterior aspects of the mid-arm to the wrist and mid-thigh to mid-calf.[1,2,3,5] Typical of the lesions of piebaldism are islands of normal and increased pigmentation within the hypomelanotic areas, and sometimes hypopigmented borders.[1,5,6] The white forelock, with a depigmented triangular patch of the scalp and forehead occurs in 80 to 90% of piebaldism individuals.[1,2,3,5]

Histology from depigmented area reveals decreased number or absent melanocytes and melanin.[2,5,6] Abnormal melanocyte cytoplasmic pattern and decreased Langerhans cell can be present.[3]

The management of this disease is the usage of the sunscreen and camuflage-hair dye, Dermablend; 20% topical monobenzyl ether of hydroquinone.[2] Sun avoidance during peak hours of ultraviolet exposure during the day, is important because recurrent sun damage may result in an increased risk of cutaneus malignancy.[1]

CASE REPORT

A 5-year-old javanese boy came to our department with depigmented patches. There were white patch on the central portion of forehead with white forelock permanently. Both of the medial eyebrows also became white. On the abdomen there was depigmented area with islands of normal patches and hypopigmented borders. A hypopigmented area on both leg symmetrically with irregular in shape, present since birth. The size and the appearance of leucoderma had remained unchanged since birth. No family history about this condition was noted. In addittion, after longer sun exposure or after swimming, the white spots become hyperpigmented and warm.

Patient is a pre-elementary school student and has no problem with his study. No complaint about defecation, vision and hearing. History of the same disease in his family was denied. The history of giving topical or/and oral treatment was denied.

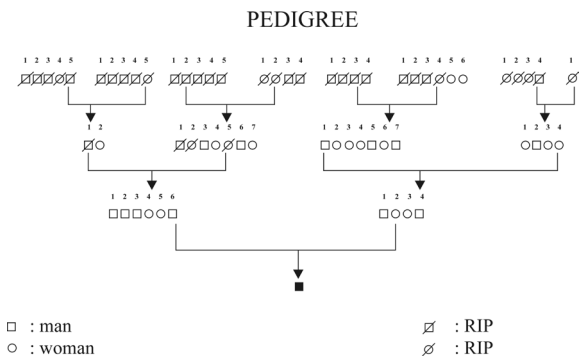

Figure 1. Pedigree from three level generation.

Physical examination on the first day of admission, showed an alert child with blood pressure 120/70 mmHg, pulse rate 80 times per minute, respiratory rate was 24 time per minute, and body temperature was 36,5° C. There were no signs of anemia, cyanotic, icteric, enlargement of lymphnode and respiratory distress. There was no dystopia canthorum (the comparate of inner and outer canthii was more than 0,6). The heart and lungs were normal and no abnormalities were found on the abdominal examination. There were no signs of oedema and his extremities were warm.

Dermatological examination from central frontal scalp revealed the white forelock and white skin on forehead. The medial eyebrows also affected symmetrically. At the upper trunk, back and buttocks area there were hypopigmented maculae in varians size 0,2 to 5 centimeter. Depigmented patches with island of normally patches within were noted at the abdomen area. White spots irreguler in shape distributed symmetrically on the leg (figure 2).

Differential diagnosis of this patient were piebaldism, vitiligo and Waardenburg Syndrome (WS).

The result of laboratory tests (blood and urine routine examination) was normal. Whereas, the result of consultation to ENT department and Opthalmologic department were normal.

The histopathology examination on skin specimen from depigmented area showed decreased number or absent melanocytes and melanosome granules at dermoepidermal junction and upperdermis with HE

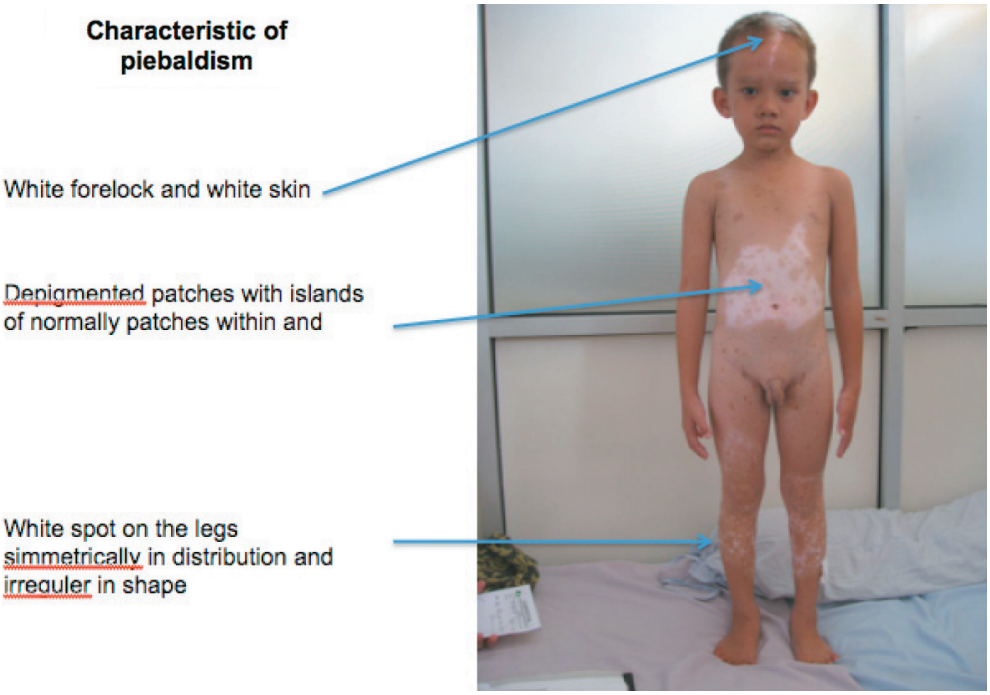

Figure 2. Typical clinical features in patient with piebaldism.

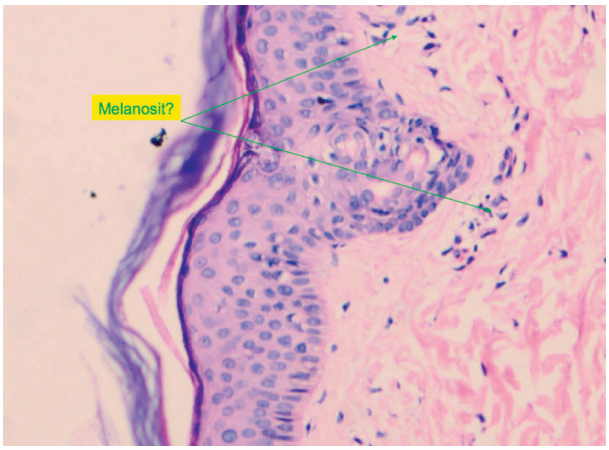

Figure 3. Histopathology feature from depigmented skin of the patient.

staining (Hematoxyllin-Eosin). Dermal condition showed infiltration lymphocyte at upperdermal and no signs of malignancy (Figure 3).

Based on history, typical clinical features, histophatology and laboratory examination the assessment of this patient was Piebaldism.

Management for this patient was education to the family member about the genetic transmission of the disorder, and given topical treatment consist of sunscreen and camouflage cosmetic. Education about the usage of sun protective measures and sun avoidance during peak hours of ultraviolet exposure during a day were also necessary.

DISCUSSION

Piebaldism (synonym: familial white spotting) is relatively rare, although its actual frequency is not know.[2,7,8] Incidence is less than 1:20,000; it can affected to all races with male and female ratio 1:1.[2] Because of its distinctive phenotype, piebaldism, sometimes incorrectly called partial albinism, has been known since at least ancient Greek times, and

was one of the first autosomal dominant genetic disorder recognized. Piebaldism was also one of the first genetic disorders for which a pedigree was presented, and several families have been reported that trace inheritance of the disorder over hundreds of years. Etymologically, pie apparently refers to the variegated black and white plumage pattern characteristic of the magpie, and bald derives from the Greek *phalios,* having a white spot.[8]

Only melanocytes are involved in piebaldism. Pigmentary disorders are limited to hair and skin without neurological, ocular, or hearing defect. The topographical distribution of the lesions spreading to the anterior part of the trunk, abdomen, extremities and the frontal part of the scalp is characteristic of the disease. The white forelock is the most frequent are depigmented. Hair and subjacent skin are depigmented. Other pigmentary defect are hypo- and hyperpigmentations that give with the adjacent normal skin a "mosaic" pattern. The hypopigmented patches can be isolated (10–20% of cases).[9]

Piebaldism is a rare autosomal dominant disorder with congenital hypomelanosis.[1,2,9,10] It means a pattern of heritance in which an affected individual has one copy of a mutant gene and one normal gene on a pair of autosomal chromosomes. Individual with autosomal dominant disease have a 50-50 chance of passing the mutant gene and therefore the disorder onto each of their children.[11] Yang Y, reported new mutation of KIT gene in two Chinese patients with piebaldism. Genomic DNA sample of the patients and their parents detected a nucleotide transversion of C1862A wich results in Ala621Asp substitution in KIT protein in patient 1 and a transition mutation of T1784C which leads to Leu595Pro substitution in patien 2. None of their unaffected parents carried the mutations. Therefore, the T1784C mutation in patient 2 is a *de novo* mutation. In addition, these two nucleotide were not found in 50 unaffected controls.[12] Simmilarly in this case there were no family history of the disease or parental consanguinity were identified, suggested that there was possibility of *de novo* mutation in the patient (Figure 1).

Cutaneus melanocytes are dendritic cells that originate during embryologic development as melanoblasts in the neural crest, whereas retinal melanocytes are derived from the optic cup. Neural crest-derived melanoblasts subsequently migrate to the epidermal/dermal border of the skin, the hair bulbs in the dermis, and the iris and choroid of the eyes. The heterogenous distribution of the skin and hair pigment characteristic of piebaldism and WS result from abberant distribution of melanocytes from neural crest to the corresponding areas of the skin or eye during development. In piebaldism, pigmentary anomalies constitute the only clinically significant feature. However, in WS, in addition to piebald-like skin depigmentation, there are characteristic abnormalities of other neural crest-derived elements, principally distopia canthorum (lateral displacement of the inner canthi) and deafness.[7]

Piebaldism resulting from mutations in c-kit proto-oncogene on chromosome 4q12.[2,13] This gene, human homologous for the murine locus *white spotting*, encodes for a tyrosine kinase receptor named c-kit.[24] Its expressed on the surface of melanocytes, mast cells, germ cells and hematopoietic stem cells. The c-kit ligand is the stem cell factor. Stem cell factor is involved in proliferation and survival of melanoblast.[9,24] A mutation in the c-kit proto-oncogene results in abnormal tyrosine kinase transmembrane receptors, decreases signal transduction, and causes abnormal melanocyte embryogenesis with defective melanoblast proliferation, migration and distribution.[2,8,14,20]

The KIT protein is a member of the tyrosine kinase family of transmembrane receptors. The KIT polypeptide consists of an amino-terminal extracellular ligand-binding receptor domain composed of five immunoglobulin-type repeats, a short transmembrane domain, and an intracellular bipartite tyrosine kinase domain consisting of bipartite tyrosine kinase domain followed by a carboxy-terminal tail (picture 4).[7,8,15]

In general, point mutations of the kit gene mutations are of four classes, associated with increasingly severe phenotypes as KIT functions is correspondingly reduced (Figure 4).[7] The most severe mutations seem to be dominant negative missense mutations of the intracellular tyrosine kinase domain, whereas mild piebaldism appears related to mutations occurring in the amino terminal extracellular ligand binding domain with resultant haplo insufficiency (Figure 4).[1,7,8,10] Nomura et al. described a novel KIT gene missense mutation (Thr847Pro) in a Japanese family with piebaldism that supportive evidence that missense mutation within the tyrosine kinase domain produces a severe phenotype.[16] Spritz et al identified c-kit gene mutations in three patients with piebaldism. A missense substitution (Phe→Leu) at codon 584, within the tyrosine kinase domain, is associated with severe piebald phenotype, whereas two different frameshifts, within codons 561 and 642, are both associated with a variable and relatively mild piebald phenotype. This is consistent with a possible "domain negative" effect

of missense c-kit polypeptides on the function of the dimeric receptor.[25]

Several pathologic mutations of the KIT gene now have been identified in different patients with piebaldism.[21] In a recent analysis reported 26 unrelated patients with piebaldism like hypopigmentation (i.e, 17 typical patients, 5 patients with atypical clinical features or family histories, and 4 patients with other disorders that involve white spotting), novel pathologic mutations or deletions of the KIT gene were observed in 10 (59%) of the typical patients and in 2 (40%) of the atypical patients. Overall, pathologic KIT gene mutations were identified in 21 (75%) of 28 unrelated patients with typical piebaldism. Patients without apparent KIT mutations had no apparent abnormalities of the gene encoding steel factor itself; however, genetic linkage analyses in 2 of these families implied linkage of the piebald phenotype to KIT. Thus, most patients with typical piebaldism seem to have abnormalities of the KIT gene. A complex network of interacting genes regulates embryonic melanocyte development.[19]

Patient with piebaldism clinically characterized by congenital and nonprogressive depigmentation of skin (leukoderma) and hair (poliosis). Its typical manifestations include a triangular white forelock and hyperpigmented macule on depigmented patches

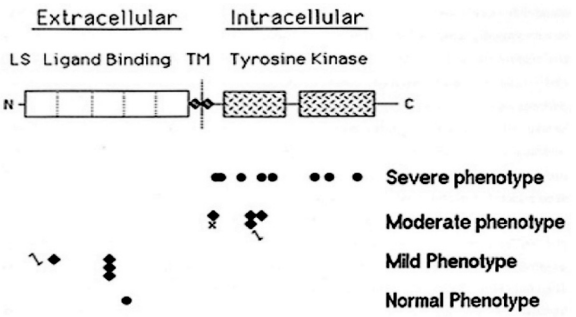

Figure 4. Locations of known KIT gene mutations associated with piebaldism. The amino-terminal extracellular leader squence (LS) and penta-repetitive ligand binding domain, the transmembrane domain (TM), and the bipartite intracellular tyrosine kinase domain are indicated. Blackened circles indicate the site of amino acid substitutions; blackened diamonds indicate the site of frameshifts; X indicate the site of a nonsense mutation; zigzags indicate the sites of splice consensus mutations
(Cited from reference number 7, 17).

and normal skin.[12] Depigmented patches are mainly found on the scalp, forehead, ventral or lateral trunk, limb and/or the mid-extremities, with the hand and feed spared.[2,3,4,12] Eyebrows and eyelashes may also be involved. Usually depigmented patches and poliosis in symmetrical distribution.[10] Poliosis is a common feature.[4] The white hair and patches of such patients are completely formed at birth and do not usually expand thereafter.[1,5,6] In this case, the patient showed typically condition features of piebaldism, like depigmented patch on the central frontal scalp with the white forelock. The medial of eyebrows also affected symmetrically. The other typical conditions were depigmented patches with island of normally patches within and at the border of hypopigmentation on the abdomen area. The white spots irreguler in shape distributed symmetrically on the legs. Both hair and skin were permanently white from birth and do not expand thereafter.

Based on the theory in the patient with piebaldism reveals that melanocytes are absent or considerably reduced in depigmented patches histologically and ultrastructurally. They are normal in number in the hyperpigmented areas.[10,12,13] Abnormal melanocyte cytoplasmic pattern and decreased Langerhans cell will be present.[3] In this case, the histopathology examination from depigmented skin area showed the same feature of piebaldism, there were decreased number or absent melanocytes and melanosome granules at dermoepidermal junction and upperdermis with HE (Hematoxyllin-Eosin) staining.

Differential diagnosis of this patient were vitiligo and Wardenberg Syndrome. Vitiligo is a multifactorial polygenic disorder with a complex pathogenesis.[4] Its an autoimmune disorder characterized by ivory-white patches secondary to melanocyte destruction. The disease is inherited as autosomal dominant with variable penetrance and is estimated to affect 1–2% of the population. Thirty percent of patients have either a positive family history of vitiligo or a history of halo nevi or premature hair graying. Vitiligo usually affects young adults, with 50% a cases occurring before the age of 20 and 25% before the age of 8 years. The disease uncommon in infancy. In most cases, symmetrical lesions develop on sun-exposed area like the dorsa of hands, the face, and neck. Other favored sites include body folds like the axilla and groin and body orifices such as the mouth, nose, umbilicus, genitals, and anus. Vitiligo lesions can also arise over bony prominences like the elbows and knees. Lesion are usually variable in size and shape

and consist a well-defined depigmented macules and patches. Loss of pigment may not apparent in fair-skinned individuals but may be disfiguring in blacks. Vitiligo can appear at sites of trauma and sunburn (Koebner's phenomenon).[22] The depigmentation of piebaldism can be differentiated from that vitiligo by the usual presence at birth, lack of convex borders, and predilection for ventral surface, in contrast to the predilection on exposed areas, body orifices, areas of trauma, and intertriginous regions of vitiligo.[1,6,17] In this case the lesion presence at birth, static in shape, size and distribution. Both depigmented of skin (leucoderma) and hair (poliosis) are permanently white since birth and do not expand thereafter. The lesion predilections are on the central forehead, eyebrows, abdomen area and both lower legs, but not at sites of trauma.

Waardenburg syndrome (WS) is an autosomal dominant disorder characterized by piebald-like pigmentary anomalies of the skin and hair, pigmentary abnormalities of the iris (heterochromia irides), lateral displacement of the inner canti of the eyes (dystopia canthorum), and sensorineural deafness. WS occurs with an overall frequency of 1 to 2 per hundred thousand, and accounts for at least 0.5 percent of cases of congenital deafness. All of the abnormalities in WS involve the neural crest, and both HSCR (Hirschsprung's disease) and neural tube defect occur at increased frequencies. WS appears to be a more general disorder of neural crest development than piebaldism.[4,7] Piebaldism is one of the cutaneous signs of Waardenburg syndrome, along with heterochromia of the irides, lateral displacement of inner canthi, and deafness.[1] In this case, the result of consultation from ENT department and Opthalmologic department did not support abnormalities of the iris (heterochromia irides), lateral displacement of the inner canthi of the eyes (dystopia canthorum), and sensorineural deafness. This supported to diagnosis of piebaldism which restricted to the hair and skin.

Management is a challenge.[10] Depigmented skin in piebaldism is generally considered unresponsive to medical or light treatment.[1] Sunscreen are recommended and simple approaches such as the use of make up or of a pigmenting agent such as the tanning product dihydroxyacetone (DHA) to camouflage exposed area are useful, although temporary.[10] Oral and topical methoxalen plus UVA were successful in inducing new hyperpigmented spot within piebald lesions, however, the cosmetic effect was largely unsatisfactory.[18] In patients who show increased pigmentation after ultraviolet exposure, phototherapy may be considered.[1,2,6] Surgical approach seem to be more promising in repigmenting localized piebald lesions.[18,26] Reepithelialization by grafting with autologous cultured epidermis after laser removal of epidermis has provided permanent repigmentation in patients.[1,2,6,27] In a retrospective study, all patient with piebaldism had excellent repigmentation with transplantation. Grafts of epidermis sheets were found to be technically easier and to yield the best results, except on elbows and arms.[10,27] To this end, complete or nearly complete repigmentation was achieved in all accordingly treated patients. Notably, the piebald lesions treated involved a sizeable area of up to 1000 cm^2.[18]

Patient and familial education about the genetic transmission of the disorder is very important. The usage of sunscreens, sunprotective measures (eg, wide-brimmed hat, long-sleeved shirts, long pants), sun avoidance during peak hours of ultraviolet exposure during the day, and self-examinations are also necessary because recurrent sun damage may result in an increased risk of cutaneous malignancy. Patients who are self-conscious about the appearance of their skin may benefit from use of a camouflage cover-up, such as dermablend or other similar camouflage measures, finally.[1,2,3,6]

Piebaldism is a benign disorder. Pigmentary alteration usually stable and permanent and patient can have normal life span. However, giving information about genetic inheritance and education of this disorder to the patients and family member must be done clearly.[1,2]

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