Red blood cell antigen changes in malignancy: case report and review

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Red blood cell (RBC) antigens represent inherited traits and as such, their expression should be constant throughout the life of an individual. We describe a patient in whom the expression of the Rh D and C antigens was lost due to the development of chronic myelogenous leukemia (CML). For this patient, this represented more than a blood bank curiosity but was of critical importance in determining further treatment of the leukemia.

The mechanisms behind changes in RBC antigens due to malignancy are reviewed for a number of antigens, antigen systems, and antigen collections. Previous case reports of RBC antigen changes due to malignancy are summarized.

Key Words: leukemia, erythrocytes, antigens, mutation, ABO blood group system, Rh blood group system, MNS blood group system, Lewis blood group system, I blood group collection, chromosome abnormalities

Case Report

A 48-year-old Caucasian woman presented to a referring clinic with a 3-month history of increasing malaise and poor energy. She had experienced recent bruising and abdominal pain. Her past medical history revealed a well adult with prior surgeries including total abdominal hysterectomy and tonsillectomy/adenoidectomy and no prior hospitalizations for medical illnesses. She was on no routine medications. She denied exposure to known marrow toxins. Her family history revealed her to be one of a set of identical twins. Significant physical exam findings included multiple bruises on the extremities and a palpable spleen. Hemogram showed a white blood cell count of 225,200/mL (normal 4,800 to 10,800/mL), hematocrit of 36.8 percent (normal 37 to 47%), hemoglobin of 12.8 g/dL (normal 12 to 16 g/dL), and a platelet count of 468,000/mL (normal 130,000 to 400,000/mL). White cell differential showed 65 percent neutrophils (normal 40 to 70%), 3 percent metamyelocytes (normal 0%), 15 percent myelocytes (normal 0%), 7 percent lymphocytes (normal 24 to 44%), 1 percent monocytes (normal 3 to 7%), 4 percent basophils (normal 0 to 1%), 4% eosinophils (normal 0 to 3%), and 1 percent blasts (normal 0%). A bone marrow biopsy and aspirate were obtained and demonstrated a hypercellular (100%) bone marrow with histologic and flow cytometric features consistent with CML. Cytogenetic analysis revealed the presence of the Philadelphia chromosome (t [9;22]), consistent with CML. No further abnormalities, including abnormalities of chromosome 1, were noted on karyotype analysis. Subsequent molecular studies from peripheral blood confirmed the presence of BCR/ABL fusion product. The patient was treated with hydroxyurea for normalization of peripheral blood counts.

Following initial presentation and management, the patient was referred to our center to be evaluated for syngeneic hematopoietic stem cell transplantation as definitive therapy for her diagnosis. The patient's physical examination and pretransplant organ function studies were normal. Results from physical examination and donor evaluation studies of the patient's sibling were also normal. The twins physically appeared to be identical. Molecular typing of the sisters for HLA revealed them to be identical (6 out of 6 match at the *HLA-A, HLA-B*, and *HLA-DR* loci). Additional molecular studies were undertaken to prove that the sisters were identical twins. These consisted of comparing four variable number of tandem repeats (VNTRs) and nine short tandem repeats (STR) loci. The two were identical at all 13 loci tested. However, ABO and Rh typing by serologic methods revealed that the patient typed as A, D– whereas her sister typed as A, D+. In order to resolve this apparent discrepancy, additional testing was performed. A new specimen was obtained from each sister that confirmed the previous ABO and Rh typing. Weak D testing with appropriate controls was

performed on the patient and was negative. An extended RBC phenotype was performed and is given below:

Patient: D–, C– E–, c+, e+, M+, N+, S+, s–, K–, k+, Fy(a+b+), Jk(a+b+)

Sister: D+, C+, E–, c+, e+, M+, N+, S+, s–, K–, k+, Fy(a+b+), Jk(a+b+)

Additional history was obtained from the patient and from review of outside medical records. As opposed to her current D– typing, the patient had typed as D+ at the birth of her second child in 1982 and also at four whole blood donations between 1984 and 1989. Therefore, further testing was initiated. Additional studies included molecular genotyping for the *RHD* gene via polymerase chain reaction. This revealed that both the patient and her sister were D+ by molecular methods (amplification of *RHD* exons 7 and 10). Finally, adsorption and elution studies using anti-D and anti-C demonstrated that the patient's RBCs could adsorb and elute both anti-D and anti-C. Taking into consideration the results of all tests and historical events recorded, we concluded that the patient and her sister were identical twins.

There are significant clinical implications surrounding the determination of identical twin status. Hematopoietic stem cell transplant (HSCT) for chronic phase (CP) CML with syngeneic versus allogeneic donor stem cells has implications on the implementation of graft-versus-host disease (GVHD) prophylaxis as well as expected outcome from therapy. No GVHD prophylaxis is warranted in the syngeneic setting. Clearly, this is not the case in allogeneic transplants in which the presence of GVHD posttransplant is readily recognized as a cause of transplant-related toxicity and mortality. Syngeneic transplantation with an effective conditioning regimen has a high probability of curing patients with CML in the CP. That said, data analyzed and published by the International Bone Marrow Transplant Registry showed identical twin transplants in CML to be associated with increased relapse risk when compared with HLA-identical sibling transplants.[1] However, they reported leukemia-free survival to be similar after twin and HLA-identical sibling transplants. This is due to the increased relapse potential in identical twin transplants being offset by decreased treatment-related mortality. Our patient remains free of hematologic, morphologic, and cytogenetic evidence of disease 100 days following syngeneic HSCT. Molecular studies of bone marrow aspirate for the presence of the BCR/ABL fusion product remain positive.

Changes in Red Blood Cell Antigens With Malignancy

Either loss or diminished expression of RBC antigens have been reported to occur in a number of malignancies (both hematologic and solid; see Table 1). The first report,[2] and those which make up the majority of reports,[3–6] have involved alterations in the expression of ABO blood group antigens. In addition to the ABO blood group system, multiple other antigens and antigen systems/collections have been reported to be affected by malignancy (see Table 1).

These changes in blood group antigens can result from a number of mechanisms; the mechanism involved depends on the antigen involved as well as on the disease. For hematopoietic diseases, the loss of expression predominantly results from a mutation within a stem cell that affects antigen production. If the affected clone gives rise to a significant proportion of the RBCs, it may result in the appearance of a mixed population of antigen-negative and antigen-positive RBCs. If the clone has given rise to all or the majority of the RBCs present, then complete loss of the antigen occurs.

ABO system

Loss or weakening of ABO antigens presents as a discrepancy in the forward and reverse typing of patients. Because ABO typing is routinely performed in pretransfusion testing, ABO antigens are the most frequently reported blood group antigen change identified in malignancy. In order to detect changes in other systems or antigens, one must either have known the patient's previous phenotype and observed a change or detect a return to their original phenotype during the course of treatment.

The production of ABO antigens results from the interactions of two glycosyl transferases. The first enzyme, *H* transferase, adds a fucose to the terminal galactose of precursor substance. The H substance generated is then acted on by the *A* and/or *B* transferases that add an N-acetylgalactosamine or a galactose, respectively.

In leukemias and other hematopoietic disorders, two possible mechanisms exist to explain the weakening of ABO antigens. In the first, the *A* and/or *B* transferase are inactivated. The result is weakening or loss of the A and/or B antigens with a concurrent increase in H antigen

Table 1. Red blood cell antigens reported to be altered by malignancy

Antigen, antigen system, or antigen collection	Effect of malignancy	Chromosomal location	Malignancies reported to be associated with changes
ABO	Decreased A and/or B with increased H Decreased A and/or B with decreased H	*A* and *B* transferase gene – *9q34* Fucosyl transferase *H* gene – *19q13*	AML CML MDS Hodgkin's disease
	"Apparent" loss of A and/or B		Gastric carcinoma Pancreatic carcinoma Ovarian carcinoma Colon carcinoma Cholangiocarcinoma
Rh	Decrease/loss of D Decrease/loss of E Decrease/loss of C Combinations of the above	*1p36*	AML CML Myeloid metaplasia Polycythemia vera Myelofibrosis Chronic myelomonocytic leukemia
Lewis	Loss of Lewis antigens	Lewis gene – *19p13* Secretor gene – *19q13*	AML CML Gastric carcinoma
Ii	Decreased I and increased i Increased i with normal I	Unknown	AML CML ALL CLL
MNSs	Loss of s	*4q28*	CML
LW	Loss of LW antigens	*19p13*	Hodgkin's disease Non-Hodgkin's lymphoma
Colton	Loss of Colton antigens	*7p14*	MDS with monosomy 7
AnWj (Anton)	Loss of AnWj	Unknown	Hodgkin's disease Non-Hodgkin's lymphoma
Cromer	Loss of Cromer antigens	*1q32*	PNH MDS
Cartwright	Loss of Cartwright antigens	*7q22*	PNH MDS
Dombrock	Loss of Dombrock antigens	*12p13*	PNH MDS
JMH (John Milton Hagen)	Loss of JMH	*15q23*	PNH MDS
Tn antigen	Expression of Tn antigen	———	AML Myelofibrosis MDS

AML: acute myelogenous leukemia; CML: chronic myelogenous leukemia; ALL: acute lymphocytic leukemia; CLL: chronic lymphocytic leukemia; MDS: myelodysplastic syndrome; PNH: paroxysmal nocturnal hemoglobinuria

because H antigen is no longer converted to A and B antigen, a finding that has seen by a number of authors.[5,7–10] It has been suggested that, at least in CML, such a change may result from inactivation of the *A* and/or *B* transferase genes on chromosome 9 through the generation of the 9;22 chromosomal translocation (Philadelphia chromosome).[11] The gene encoding the *A* and *B* transferases is located at 9q34, the area in which the break point for the chromosomal translocation occurs. As a result, the translocation could disrupt the gene, thereby preventing expression of the transferase. Although this is a possibility, ABO changes are more commonly seen in acute myelogenous leukemia (AML), where this chromosomal translocation is uncommon.[9]

One study of 12 patients with acute myelogenous leukemia (AML) and weakening of the ABO antigens suggested that the *ABO* gene inactivation was not random. In four of four patients studied, only the maternally derived *A* or *B* gene was affected. This suggested the presence of genomic imprinting, defined as the differential expression of a gene as determined by whether it is inherited from the mother or father, in determining which gene was inactivated. The authors of this report realized that additional study was needed, given the small number of patients examined.[12]

The second possible mechanism for the loss of ABO antigens involves the inactivation of the *H* transferase encoded at 19q13. The loss of *H* transferase would result in decreased H substance and a resulting decrease in *A* and/or *B* substance, again identified in a number of patients.[7,9–13]

Loss of ABO antigens is of more than academic interest. In a number of cases, the loss or weakening of ABO antigens has been detected prior to the diagnosis of the underlying hematopoietic malignancy, frequently in the setting of long-standing myelodysplasia.[10,14,15] It has been suggested that the identification of a loss of ABO antigens should result in the search for an underlying hematopoietic malignancy. Finally, changes in ABO antigens have also mirrored the course of the malignancy with return of the original blood type upon remission and reappearance of antigen-negative cells with recurrence.[6–16]

In the case of solid tumors such as pancreatic, gastric, colonic, ovarian, and biliary carcinomas, an apparent loss of ABO antigens also can be seen.[16] The term "apparent" is used because unlike in hematopoietic malignancies, the number of *A*, *B,* and *H* antigens on the RBCs is not altered. Instead, the tumors secrete large amounts of soluble *A* and/or *B* substance. The soluble blood group substance that neutralizes the typing reagents resulting in the apparent loss of A and B antigens can be overcome by washing the RBCs thoroughly prior to forward typing in order to remove the plasma with its soluble blood group substance.[17]

This finding is usually detected as a discrepancy between the forward and reverse typing of the patient.

Rh system

The loss or weakening of the D antigen, after ABO, is the second most commonly reported change in blood group antigens. Again, this may be because the presence or absence of D is routinely determined and therefore changes are noted. In addition to the loss of D,[18–24] loss or weakening of other Rh system antigens including C and E have been reported.[25–28] Frequently, this has occurred with concurrent loss or weakening of D.[25,27,28] Patients have presented either with a complete loss of selected Rh system antigens[20,23–25,28] or with the development of a mixed population of antigen-positive and antigen-negative cells (frequently referred to as mosaicism).[18,19,21,22,26,27]

The antigens of the Rh system are multi-pass proteins encoded by two genes located at 1p36. The *RHD* gene encodes the antigen D whereas the *RHCE* gene encodes the antigens C, c, E, and e. Rh negative individuals either lack the *RHD* gene or have mutations within the gene that prevent D antigen production. The mechanism of the loss or weakening of D and the other Rh antigens is thought to be disruption or mutation of these genes. In three reported cases of loss of the D antigen, chromosomal abnormalities involving either the entire chromosome 1[26] or the short arm of chromosome 1[20,23] were seen on cytogenetic analysis. These were thought to be responsible for the loss of antigen expression through deletion or disruption of the *RHD* gene. In another report,[24] cytogenetic abnormalities were not identified but sequencing of the *RHD* gene revealed a single base pair deletion within the gene. This deletion resulted in a frameshift and a premature stop codon, eliminating production of the D antigen.[24]

As with changes in ABO antigens, changes in Rh antigens have been reported to mirror the course of the disease.[21,23,25] When patients enter remission, their original Rh phenotype returns, whereas antigen-negative cells reappear during relapse.

In one reported case, the disappearance of the D antigen was associated with the subsequent development of anti-D.[20] This patient suffered from myeloid metaplasia, a chronic myeloproliferative disorder, and was noted to have lost expression of the D antigen at age 37; he had been typed as D+ at age 33. Twenty years later, at age 57, he was found to still be D– but had developed anti-D as well as anti-C. The authors postulated that because of the prolonged course of the illness, the patient lost tolerance to the D antigen.[20]

Lewis system

Lewis antigens are not intrinsic to the RBC surface but are adsorbed onto the surface of RBCs from the surrounding plasma. Lewis antigens are produced by the interactions of two fucosyltransferases. Le^a is produced when the fucosyltransferase encoded by the Lewis gene (*Le*) at 19q13 adds a fucose to type 1 chain. In the presence of the secretor gene (*Se*), a fucose is added to the terminal galactose of the type 1 chain to generate type 1 H substance. This substance can then be acted upon by the Lewis gene (*Le*) to produce Le^b.

As Lewis antigens represent extrinsically acquired RBC antigens, it would not be expected that hematologic malignancies would affect the expression of Lewis antigens. Cases of loss of Lewis antigens with leukemia have been reported.[3,29] The mechanism behind this loss is unknown but the authors of these reports postulated that the loss of the ABO antigens in these patients may have interfered with the binding of soluble Lewis substance to the red blood cell surface.[3,29]

Abnormalities of RBC Lewis antigens adsorbed onto RBCs also have been reported with gastric carcinomas. An increased frequency of Le(a–b–) phenotype has been seen in gastric cancer patients (16% versus 6.3% of healthy controls).[30] It was therefore thought that the Le(a–b–) phenotype represented a risk factor for the development of gastric carcinoma. Csato et al.[30] examined the saliva of Le(a–b–) gastric cancer patients and healthy controls for the presence of Le^a antigen and discovered 55.3 percent of the Le(a–b–) gastric cancer patients secreted Le^a antigen in their saliva versus 4.3 percent of healthy controls. This indicated that half of the Le(a–b–) gastric cancer patients possessed the *Le* gene and therefore should have at least Le^a substance on their RBCs, depending upon their *Se* gene status.[30]

Ii collection

I and i antigens are located on the subterminal portions of the oligosaccharides that are converted to H and subsequently A or B antigens. The chromosomal location of the genes encoding the production of these oligosaccharide antigens is unknown. The I antigen is found in 99.9 percent of adults but is not found on cord RBCs. Conversely, i is present on cord RBCs but is poorly expressed in adults. During the first 2 years of

life, the amount of I present on RBCs increases while the amount of i decreases in a reciprocal fashion.

Changes in the level of I and i antigens, both increases and decreases, have been reported in association with leukemia. Schmidt et al.[31] reported decreases in I antigen among 30 percent of patients with CML, AML, chronic lymphocytic leukemia (CLL), and acute lymphocytic leukemia (ALL). Others have also reported a decrease in I antigen.[3] Jenkins et al.[32] and Kolins et al.[29] reported not only a decrease in I in patients with leukemia, but also a reciprocal increase in i. The mechanism behind these changes is uncertain but may represent a response to hematopoietic stress,[32] as an increase in i with a stable expression of I has been reported to occur in some nonneoplastic diseases.[33] Alternately, it has been suggested that loss of specific transferases may occur or that failure to form normal antigen configurations of ABH, Lewis, and I antigens may result in antigen loss.[3,29,32] Jenkins et al.[32] found weakening of the A antigen in addition to decreased I antigen and increased i antigen. In the cases reported by Kolins et al.[3,29] in 1978 and 1980, ABH and Lewis antigens were also lost.

MNS system

MNS are antigens located on glycophorins A and B, which are single-pass transmembrane glycoproteins. The genes encoding these antigens, *GYPA* and *GYPB*, are located at 4q28.

A single report has appeared where the weakening of s antigen was noted in a patient with CML.[21] The patient presented with CML and was noted to demonstrate mixed field typing for D antigen. Extended red blood cell antigen typing showed the patient to be M+, N–, S+, and s–. Subsequent evaluation of the MNSs phenotypes of the patient, his wife, and their children suggested that the patient should be s+. Microscopic examination of the patient's RBCs using different anti-s reagents demonstrated mixed-field agglutination. Adsorption and elution studies similarly demonstrated the presence of the s antigen.[21] A Philadelphia chromosome was noted in this patient but abnormalities of chromosome 4, the location of the gene coding for this antigen, were not seen.

Landsteiner-Wiener (LW) system

LW system antigens are glycoproteins similar to adhesion molecules and are encoded by a gene located at 19p13. They are intimately associated with Rh system antigens and are a part of the complex formed by Rh system antigens on the RBC membrane.

Two reports of loss of LW antigens and concurrent development of anti-LW in association with hematologic malignancies have appeared. The first report involved a patient with mixed cellularity Hodgkin's disease. At the time of presentation with his illness, he was found to have anti-LW and his RBCs were LW–. Approximately 1 year later, he was found to be LW+ and his anti-LW was no longer detectable.[34] The second report involved a patient with a T-cell non-Hodgkin's lymphoma. Again, the patient was noted to have an antibody that was identified as anti-LW^a. RBC typing revealed her RBCs to be LW(a–). Following chemotherapy and remission of her lymphoma, the patient was noted to have lost her anti-LW^a and to type as LW(a+). Subsequently, her lymphoma recurred and she was again noted to be LW(a–) with anti-LW^a. Again, remission was obtained, her antibody disappeared, and the antigen reappeared.[35]

The mechanism behind the decreased expression of LW antigens is unknown. In addition to the cases reported above, the loss of LW antigens with the development of anti-LW also has been seen during pregnancy[36] and in association with autoimmune diseases.[37]

Colton system

Colton system antigens are found on the membrane portion of the RBC water transporter, CHIP-1. They are encoded by a gene located at 7p14.

Loss of the Colton system antigen Co^a has been reported in the setting of myelodysplastic syndrome with monosomy 7, a common chromosomal abnormality in this disorder. The association was initially identified in two of five patients with monosomy 7.[38] Because Co^a is a high-incidence antigen, the absence of expression in these patients suggested an association. Additional patients were subsequently identified.[39,40]

The mechanism behind the loss of Co^a antigen is unknown. It is difficult to explain how loss of only one copy of a gene could result in loss of antigen expression given the fact that the patients still possess another copy on the other chromosome 7. Possibilities could include mutations in the other Colton gene or genomic imprinting with silencing of the other gene. Even more difficult to explain is the finding of Pasquali et al.[40] that only patients with monosomy 7 who had not received transfusions prior to testing lacked Co^a antigen. The authors postulated that either the transfusion of Co(a+)

RBCs prevented recognition of RBCs weakly expressing Co[a] or that the transfusions somehow resulted in the expression of the antigen on the patient's RBCs.

AnWj (Anton)

AnWj (Anton) is a high-incidence antigen and is the receptor for *Haemophilus influenzae*. The location of the gene encoding AnWj is unknown but the antigen is carried on CD44 proteoglycan.[41]

A single case of loss of the AnWj antigen and concurrent development of anti-AnWj has been reported. The patient was a male with Hodgkin's disease. At presentation, an antibody was identified in his serum that reacted with all RBCs. Subsequently, this was identified as anti-AnWj and the patient was found to be AnWj–. Six months after the initiation of therapy, the patient went into remission. At that time, anti-AnWj was no longer detectable and his RBCs typed as AnWj+.[42]

Cromer, Yt, and Dombrock systems, JMH antigen

Cromer, Yt, and Dombrock system antigens, as well as the high-incidence antigen John Milton Hagen (JMH), are encoded by different genes on different chromosomes. Cromer antigens are located on the complement regulatory molecule CD55, whereas Yt antigens are located on RBC acetylcholinesterase. The functions of the molecules carrying Dombrock system antigens and the JMH antigen are unknown. While representing a heterogeneous group of antigens, they do share one common feature: they are all attached to the RBC membrane by glycosylphosphatidylinositol (GPI) anchors.

Paroxysmal nocturnal hemoglobinuria (PNH) is a disorder characterized by hemoglobinuria, thrombosis, and bacterial or fungal infections. In 25 percent of cases, it can evolve into aplastic anemia and in 5 to 10 percent of cases, it can progress to AML.[43] The biochemical defect in PNH is a stem cell mutation leading to the loss of the GPI anchors with resulting loss of proteins requiring this for membrane attachment. As a result, antigens of the Cromer, Yt, and Dombrock systems as well as the JMH antigen are lost from RBCs in PNH. In fact, the loss of Cromer antigens is intimately involved in the hemolysis seen in this disorder. Cromer antigens are epitopes on CD 55, also called decay-accelerating factor. CD55 and CD59, membrane inhibitor of reactive lysis, are responsible for inactivating complement that accumulates on RBCs. The loss of these molecules results in complement build up and complement-mediated cell lysis of the RBCs.[43]

In addition to occurring in PNH and aplastic anemia, loss of GPI-anchored proteins also has been seen in 23 percent of myelodysplastic patients.[44] These patients also will demonstrate loss of Cromer, Yt, and Dombrock system antigens as well as the JMH antigen. Identification of these patients is important because many will respond to immunosuppressive therapy, which is a therapy used for aplastic anemia but one not commonly used for myelodysplasia.[44]

Tn antigen

Tn antigen is a cryptic antigen that is present in the tetrasaccharide side chains attached to glycophorins A and B of the RBC membrane. Its expression results from the loss of the enzyme 3-ß-D-galactosyltransferase (T transferase) due to somatic mutation within the bone marrow stem cells.[45] All normal adult sera contain antibodies that recognize Tn, resulting in polyagglutination of RBCs expressing the antigen. In addition, Tn antigen is similar to A antigen and can react with anti-A and anti-A,B.[46] As in the case of loss of A and B antigens, the result is discrepant forward and reverse typings. Tn antigen activation can be identified by its pattern of reactivity with a variety of lectins. This can be used to distinguish Tn expression from other causes of polyagglutinability. Tn activated cells are agglutinated by *Dolichos biflorus*, *Glycine max*, *Salvia sclarea*, and *Salvia horminum* but not *Arachis hypogaea*.[46]

Tn antigen expression has been associated with leukemia,[47–49] myelodysplasia,[50] and myelofibrosis.[51] In a study examining bone marrow and peripheral blood of normal individuals and patients suffering a variety of hematologic disease, Roxby et al.[49] found no evidence of Tn activation in 35 normal subjects and expression in 5 of 725 patients with hematologic disease. Of these five, only two were detectable by polyagglutination alone. Both of these patients had AML and both exhibited increases in the number of RBCs expressing Tn antigen as their leukemias progressed. In both patients, all RBCs expressed Tn antigen at the time of death due to their disease.[49] The remaining patients expressed low levels of Tn-positive RBCs detectable only with immunohistochemical staining.[49] It has been suggested by some authors that clones expressing Tn antigen may have a growth advantage and that this may explain in some cases why there is a progressive increase in the number of Tn-expressing RBCs.[48]

Summary

Changes in RBC antigen phenotype rarely occur. They are most frequently seen in association with hematologic malignancies but can be seen in association with solid tumors as well. The identification of these changes represents more than just an academic exercise. Changes have been identified prior to the diagnosis of the responsible underlying malignancy and have heralded relapse of the malignancy. In addition, the realization that Rh D had been lost in our patient and that the patient and her sister were identical twins avoided additional therapy that would have resulted in a significantly increased risk to the patient of morbidity and mortality. For these reasons, it is important for blood bank professionals to be aware of the existence of this phenomenon.

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